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The Journal of Allergy

VOL. 16 MAY, 1945 No. 3

American Academy of Allergy

First Annual Meeting, New York, N. Y., Dec. 11 and 12, 1944

(Continued)

TREATMENT OF RAGWEED POLLINOSIS WITH ANTIGEN-ANTIBODY MIXTURES*

PRELIMINARY REPORT

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CLEVELAND, OHIO

IT SEEMED important, in view of the properties of the thermostabile antibody, to determine whether a mixture of antigen and this antibody could be more successfully employed in the treatment of hay fever than the methods at our disposal at the present time. If this procedure proves successful, it might simplify the treatment of pollinosis by reducing to a minimum the number of injections a patient would require for treatment. The techniques employed for the production and standardization of the antibody-antigen mixtures are discussed.

TECHNIQUE

Preparation of Thermostabile Antibody Sera.—Ten per cent ragweed extract (40,000 PTA units per milliliter) was injected subcutaneously at weekly intervals into normal individuals in doses of 0.5 ml., 1 ml., 2 ml., and 4 ml. (a total of 7.5 ml. or 300,000 PTA units). Seven days following the last injection, a blood sample was taken, and the serum was titrated for thermostabile antibody content. If the titer was adequate, the subject was then bled. If it was not considered high enough, an interval of three weeks was allowed to elapse before another dose of 4 ml. of the ragweed extract was administered and then, seven days later, the subject was bled. Globulin was separated from the serum by dialysis fractionation with ammonium sulfate at 1° C. and was then lyophile-dried. The globulin was titrated for its thermostabile antibody content, and an amount of ragweed extract was added which was computed to be the quantity that would be neutralized by this antibody.

Testing for Free Antigen.—These mixtures were tested for the presence of free antigen by Johnson and Alexander's[1] modification of the serum precipitation technique first described by Hampton et al.[2] and by endermal testing of ragweed-sensitive patients. The skin tests frequently detected the presence of free antigen in sera which had been found neutralized by the precipitin technique. This discrepancy is due to the fact that the precipitin method was not sufficiently sensitive to

*Read before the First Annual Meeting of the American Academy of Allergy, New York, Dec. 11, 1945.

TABLE I

THERMOSTABILE ANTIBODY RESPONSE TO ANTIGEN-ANTIBODY MIXTURE IN A NONSENSITIVE SUBJECT

DATE	12/1/43	12/5/43	12/9/43	12/30/43
UNITS OF "NEUTRALIZED" RAGWEED EXTRACT	5,000	5,000	10,000	*Total Units* 20,000
APPROXIMATE AMOUNT OF UNNEUTRALIZED RAGWEED EXTRACT				600 to 700
THERMOSTABILE ANTIBODY TITER				750 Units

detect less than approximately 100 PTA units of free antigen. The amount of free antigen present was estimated by titrating the skin of ragweed-sensitive persons and was established as being between 10 and 100 PTA units per milliliter. These neutral or practically neutral mixtures were then injected into ragweed-sensitive individuals to determine whether the union of antigen and antibody would be dissociated with a rapidity sufficient to cause systemic reactions. Single doses containing as much as 6,000 units of "neutralized" antigen failed to produce such reactions.

Testing for Production of High Antibody Titers.—After it had been determined that the "neutralized" antigen-antibody mixtures could safely be injected into sensitive patients, it then became important to determine whether the mixtures were capable of stimulating the production of high thermostabile antibody titers.

Accordingly, a nonragweed-sensitive man was injected with amounts of an antigen-antibody mixture which totaled 20,000 PTA units of "neutralized" extract. This amount was given in divided doses over a period of nine days. In 20,000 PTA units of this particular mixture, the patient received an estimated total of between 600 and 700 PTA units of unneutralized ragweed extract. The dosage schedule and the thermostabile antibody content of this patient's serum is shown in Table I.

Since it is unlikely that the antibody titer level attained in this individual could have been the result of the estimated 600 to 700 units of unneutralized ragweed extract which he received, it seems that antibody "neutralized" mixtures are capable of stimulating the production of thermostabile antibody in nonsensitive individuals. The next step in the investigation was the administration of the mixtures to ragweed-sensitive patients. The following case histories illustrate our experiences in the therapeutic administration of these antibody antigen mixtures.

CASE REPORTS

CASE 1.—E. B., female, aged 29 years, had perennial asthma of mild character since she was 1 year old. At about 7 years of age she began to have severe exacerbations during the ragweed season. She was first seen on July 16, 1943, in an attack which had begun on June 19, 1943. Skin tests gave positive reactions to house dust, chicken feathers, and grass and ragweed pollen. The skin test to the 400 PTA unit strength ragweed extract gave a moderate reaction. She had never received specific therapy. Treatment was begun and carried out as shown in Table II.

TABLE II

TREATMENT AND RESULTS IN A PATIENT WITH ASTHMA DURING THE RAGWEED SEASON

DATE	7/16/43	7/19/43	7/26/43		7/29/43	8/2/43	8/5/43	8/9/43	
UNITS OF "NEUTRALIZED" EXTRACTS	700	2,800	5,000	*Total* 8,500					
UNITS OF UNNEUTRALIZED EXTRACTS					200	800	1,600	2,000	*Total* 4,600
REACTIONS	None	None	None		None	None	None	Systemic reaction controlled with epinephrine	
CLINICAL RESULTS	Excellent. No asthma during 1943 ragweed season.								

Our experience with this case indicated that the mixtures are not altered or dissociated in the body with a rapidity sufficient to produce reactions. This patient received 5,000 units of antibody-neutralized extract on July 26, 1943, without reaction, whereas, 2,000 units of unneutralized extract given on Aug. 9, 1943, produced a systemic reaction requiring epinephrine for relief.

CASE 2.—V. S., female, aged 29 years, was first seen in 1928 with a history of asthma since infancy. The skin testing revealed milk as the etiological factor, and symptoms were controlled with a milk-free diet. She was next seen in 1936 at the age of 21 years with recurrence of asthma during the summer and fall pollen seasons. The patient refused treatment, and symptoms recurred each year. In September, 1940, she again presented herself during an acute attack of asthma. Treatment with ragweed extract was instituted and was continued perennially for only one year. Symptoms recurred in May, 1943. Skin and ophthalmic tests done on July 16, 1943, were moderately positive to the 100-unit ragweed extract. The endermal test was negative to the 4,000-unit "neutralized" extract. Treatment was begun at that time and was carried out in the manner shown in Table III.

There was complete prevention of ragweed asthma and only occasional periods of nasal stuffiness.

No further treatment was given until July 17, 1944, when the second series of injections was begun. The total dosage of this series was 16,000 units which was given according to the dosage schedule shown in Table III.

No evidence of asthma was noted during the ragweed season of 1944. Titrations carried out on serum taken on Oct. 26, 1944, showed the thermostabile antibody titer to be 500 units.

TABLE III

TREATMENT AND RESULTS IN A PATIENT WITH ASTHMA DURING RAGWEED SEASON

DATE	7/16/43	7/22/43	4/27/43	8/10/43	
UNITS "NEUTRALIZED" EXTRACT	3,500	4,200	3,000	6,000	*Total* 16,700
REACTIONS	None	None	None	None	
CLINICAL RESULTS IN 1943	No asthma during ragweed season. Occasional periods of nasal congestion				
DATE	7/17/44	7/20/44		10/26/44	
UNITS "NEUTRALIZED" EXTRACT	4,000	12,000			*Total* 16,000
REACTIONS	None	None			
CLINICAL RESULTS IN 1944	No evidence of asthma noted				
THERMOSTABILE ANTIBODY TITRATION				500 Units	

The comparison of clinical results in this one case during two successive years suggests the therapeutic possibilities of the "neutralized" antigen mixtures. The fact that production of thermostabile antibody is stimulated in the sensitive individual by such mixtures is also established by the antibody titer in this case.

CASE 3.—H. H., female, aged 44 years, had perennial asthma of twenty years' duration with exacerbations in the tree, grass, and ragweed seasons. Perennial treatment with oak, sycamore, timothy, and ragweed pollens along with house dust had been carried out for two years with moderately good results. Treatment with grass and ragweed pollens was discontinued in September, 1943. The tree and house dust therapy was continued perennially. On May 5, 1944, 5,000 units of "neutralized" grass pollen were given without reaction. On May 10, 5,000 units were again administered, making a total of 10,000 units of "neutralized" mixture. An unusually comfortable grass season followed. On August 1, 2,000 units of "neutralized" ragweed extract were given, and, on August 5 and 10, respectively, 7,500 units were given without reaction. No exacerbations of asthma occurred during the 1944 ragweed season.

The results in this case give further evidence that treatment with the antigen-antibody mixtures may give good clinical results.

TABLE IV

TREATMENT AND RESULTS IN A PATIENT WITH ASTHMA DURING THE GRASS AND RAGWEED SEASON

DATE	5/5/44	5/10/44		8/1/44	8/5/44	8/10/44	
UNITS OF "NEUTRALIZED" EXTRACT (TIMOTHY)	5,000	5,000	*Total* 10,000				
CLINICAL RESULTS	Unusually good grass season						
UNITS OF "NEUTRALIZED" EXTRACT (RAGWEED)				2,000	5,000	7,500	*Total* 14,500
REACTIONS	None	None		None	None	None	
CLINICAL RESULTS				No exacerbations of asthma during ragweed season			

SUMMARY

1. Mixtures of thermostabile antibody and pollen extract which were approximately neutral or contained not more than 100 units of free antigen per milliliter were prepared.

2. These mixtures stimulated the production of thermostabile antibody in both normal and pollen-sensitive individuals.

3. The mixtures were administered to sensitive patients in individual doses containing as much as 12,000 PTA units of "neutralized" antigen without systemic reactions.

4. Three pollen-sensitive persons treated with these mixtures obtained good clinical results with only three to four injections of the material.

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A STUDY OF THE FUNGUS CONTAMINANTS OF THE AIR OF SAN DIEGO AND VICINITY*

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AEROMYCOLOGIC studies by investigators throughout the United States have revealed certain similarities in the fungus content of the air in many localities, but in certain instances marked contrasts have been shown. For example, Schonwald[1] found that *Rhizopus, Penicillium,* and *Trichoderma* predominated, in the order named, in the air of Seattle, whereas the genera of prime importance in most other parts of the United States, namely, *Alternaria* and *Hormodendrum,* as found by Morrow and co-workers[2] and by many other authors, were of minor incidence. Schonwald ventured the opinion that "there is probably not a great difference in the species of fungus spores all along the Pacific Coast." Aside from the data for Los Angeles included in the nationwide study, by the slide method, of *Alternaria* and *Hormodendrum* spores by Durham,[3, 4] the literature reveals no study of this problem applicable to Southern California.

Studies of the pollen content of the air of San Diego[5] and vicinity[6] demonstrated that our problem here differs from that of any other locality so far reported. It was also shown that there were marked qualitative and quantitative differences at various points within the city of San Diego as well as at different points in the surrounding area. It seemed probable, therefore, that there would be similar differences in the concentration of air-borne fungi.

Certain geographic and meteorologic data concerning San Diego and vicinity are essential to an understanding of the problem:

1. The mean annual temperature variation in San Diego is only about 13° F. However, diurnal variations of as much as 40° F. may occur. Killing frosts are unknown.
2. The annual rainfall varies from 5 to 25 inches, but averages about 10 inches, and is almost entirely confined to the winter months.
3. The relative humidity averages 75 per cent.
4. The wind is from the ocean about 90 per cent of the time, and it averages about 7 miles per hour, rarely exceeding 20 miles per hour.
5. The coast range lies to the east of San Diego, rising to as high as 6,500 feet. Numerous inland valleys and mesas intervene. Seasonal variations in climate occur in the mountains.

PROCEDURE

It has been repeatedly pointed out by other authors that both the slide method and the plate method of sampling air for fungus contamination have certain advantages as well as disadvantages. More complete information is obtained by combining the two methods.

From the Rees-Stealy Medical Research Fund, Ltd., 2001 4th Ave., San Diego, Calif.
*Read before the First Annual Meeting of The American Academy of Allergy, New York, Dec. 11, 1944.

Slide Counts.—Slides coated with the emulsion recommended for pollen studies by Wodehouse[7] were exposed daily on the roof of a two-story building in the central part of San Diego throughout the years 1940, 1941, and 1942. Graphs of the identifiable fungi found on the slides for 1941 are shown in Chart 1. The values represent the spores found on 1 square inch of slide after a twenty-four-hour exposure.

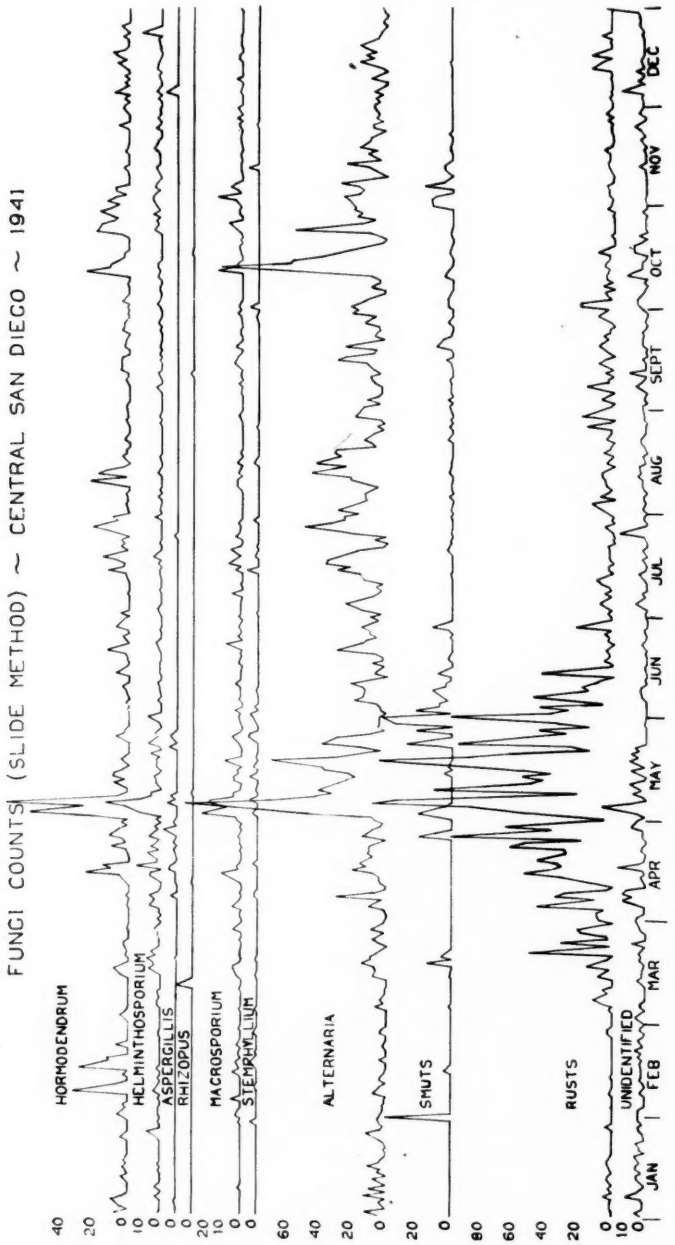

Chart 1.—Fungi counts (slide method), Central San Diego, 1941.

Graphs for 1940 and 1942 are quite similar and hence are not reproduced here. This similarity is in contrast to the findings of Bernstein and Feinberg[8] in Chicago who observed marked annual variations over a five-year period. It will be noted that fairly well-marked vernal peaks occur in each curve in which the numbers are sufficient to be significant, but that there is no time of the year when the spores of any genus are

TABLE I

RELATIVE FREQUENCY OF AIR-BORNE FUNGI IN SAN DIEGO COUNTY

1941

	PLATE COUNT (%)	SLIDE COUNT (%)		PLATE COUNT (%)	SLIDE COUNT (%)
Hormodendrum	37.5	11.1	Aspergillus	0.7	0.6
Alternaria	10.2	34.6	Pringshaemia	0.6	
Sterile mycelia	9.6		Stemphyllium	0.6	2.7
Penicillium	6.9		Helminthosporium	0.5	4.3
Sporotrichum	5.2		Fusarium	0.5	
Macrosporium	5.2	4.0	Plinozythia	0.4	
Botrytis	2.9		Rhizopus	0.2	0.1
Epicoccum	2.0		Unimportant*	12.7	
Pleospora	1.4		Rusts		32.7
Chaetomium	0.8		Smuts		4.5
			Unidentified	2.1	6.8

*Includes: *Monilia sitophilia, Cephalosporium, Mucor, Scopulariopsis, Trichoderma, Acrothecium,* and *Stachybotrys.*

TABLE II

MOLD FREQUENCY, SAN DIEGO COUNTY*

1941

(Plate Method)

	BEACH	CENTRAL SAN DIEGO	EAST SAN DIEGO	ALPINE	PATTERN†
Total Counts	3,561	4,381	6,156	7,116	R
Hormodendrum	950	1,342	2,188	3,485	R
Alternaria	200	505	804	661	R-A
Sterile mycelia	284	429	550	792	R
Penicillium	690	305	304	176	I
Sporotrichum	239	382	168	321	E
Macrosporium	160	283	488	181	R-A
Botrytis	64	122	275	155	R-A
Epicoccum	26	88	193	119	R-A
Pleospora	33	73	155	41	R-A
Chaetomium	70	47	43	21	I
Aspergillus	30	65	33	35	E
Stemphyllium	28	29	37	40	R
Pringshaemia	21	40	35	34	E
Fusarium	24	16	29	43	E
Helminthosporium	16	29	40	22	R-A
Plinozythia	42	24	24	13	I
Rhizopus	5	20	23	12	R-A
Monilia	1	19	15	15	E
Mucor	11	6	5	17	
Trichoderma	2	2	3	0	
Yeasts, etc.‡	788	527	345	361	1-A

*Sum of daily counts (twenty-minute exposure) for one year.

†R, regular—counts increase from beach to Alpine.
I, inverse—counts decrease from beach to Alpine.
R-A, counts regular except for a drop at Alpine.
I-A, counts inverse, except for a rise at Alpine.
E, erratic.

‡Yeasts, approximately 75 per cent; Torula and Candida, 20 per cent; Bacteria less than 5 per cent.

absent. The sharp variations from day to day are of interest in view of the observations of Waldbott and Asher,[9, 10] that the symptoms of hay fever and asthma do not depend so much on the quantity of pollen or spores in the air as on the rapidity of increase and decrease in concentration. It should be emphasized that the curve for *Hormodendrum* represents many large clumps as well as individual spores, and hence the total number of spores is far greater than shown. There were marked variations in the number of spores in each clump, but the average for a large number of clumps was found to be about thirty. Over a period of a year the clumps constituted 20 per cent of the total. Hence,

by multiplying the values for *Hormodendrum* in the graph by seven, a rough approximation of the total is obtained.

Plate Counts.—Ninety-millimeter Petri dishes containing Sabouraud's medium (pH 5.6) were exposed at 8 A.M. at weekly intervals on the roof of a two-story building in the central part of San Diego throughout the year 1940. A twenty-minute exposure time was found to be the

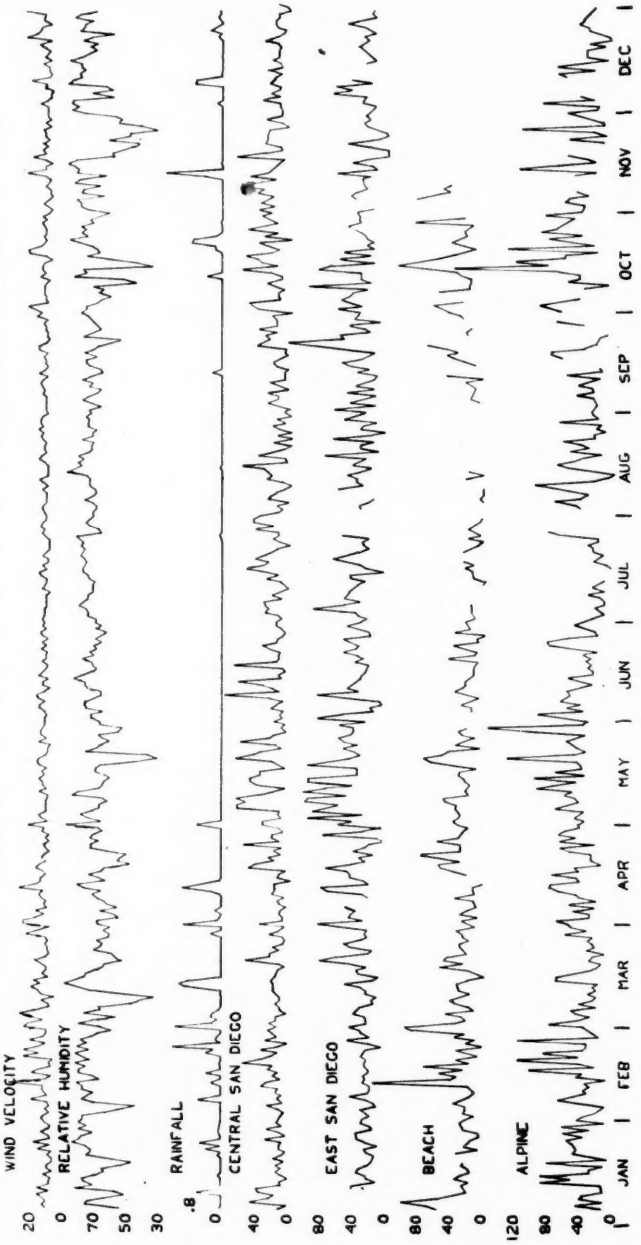

Chart 2.—Total mold counts (plate method), San Diego County, 1941.

maximum period after which it was feasible to identify the colonies which developed. Careful study of plates exposed every two hours throughout the day and night disclosed no marked or consistent variations at different hours. However, those exposed at 8 A.M. seemed somewhat less erratic from day to day. Likewise, exposures at various levels and on various sides of the building produced no constant and significant

variations. The study for the entire year of 1940 was in the nature of a preliminary survey for the more intensive studies to follow.

During 1941, plates were exposed daily at four different points, one at the beach, another in the central part of San Diego, as before, a third at the eastern city limits, and a fourth near Alpine, California, 32 miles inland at an elevation of 2,300 feet. Because of the prevailing westerly winds, it was felt that this arrangement would produce a progressive increase at each station, in the order named, for any spores produced uniformly throughout the area.

Plate exposures were continued at the central station throughout 1942 to provide information for comparison with the two previous years as well as further comparison of the plate and slide methods.

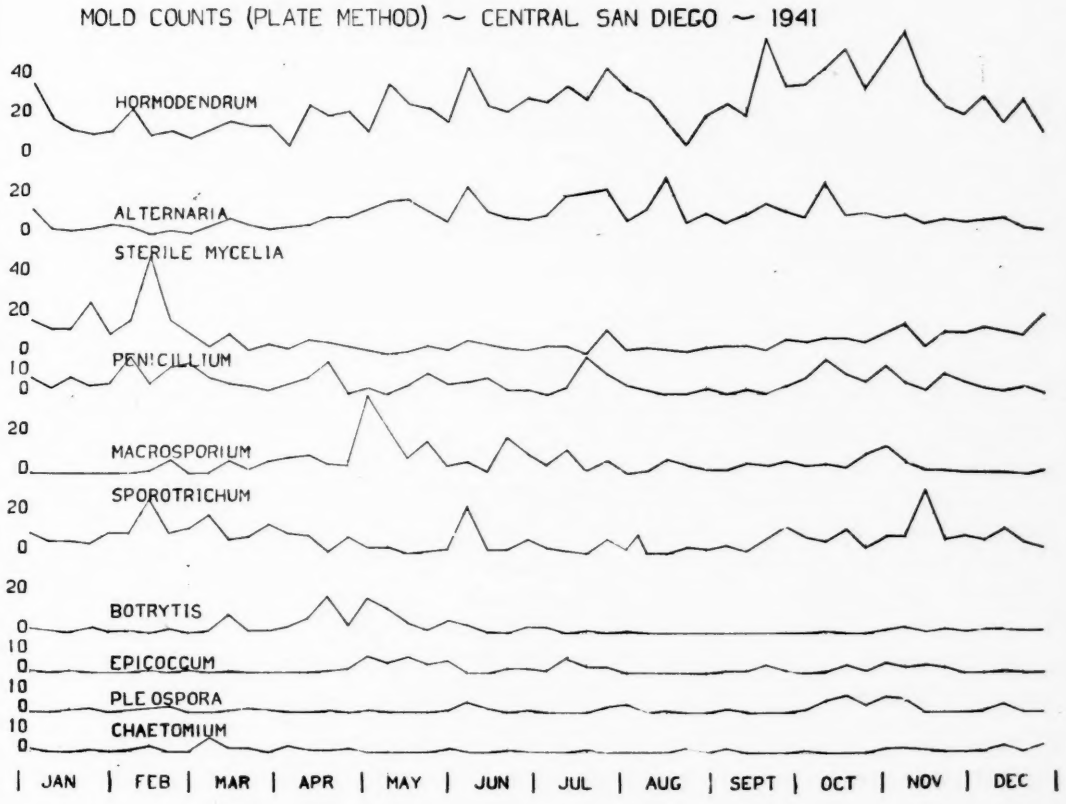

Chart 3.—Mold counts (plate method), Central San Diego, 1941.

Chart 2 shows the total mold colony counts for the year 1941 at the four collecting stations described, and Chart 3 shows the counts for the more important genera which were found at the central station for 1941. It will be seen that the counts are very erratic, even when plotted at weekly intervals, so that the curves do not reflect the seasonal trends seen in the slide counts.

A few plates were exposed from time to time on a fishing vessel at distances of from 5 to 30 miles offshore from San Diego. The types and numbers of colonies were quite similar to those obtained at the beach even though the wind was from the sea in each instance. Likewise, several plates were exposed in Imperial Valley, California. In the

irrigated central portion of the valley a predominance of yeast was found; the remaining colonies were similar to those found in San Diego. The plates exposed in the uninhabited portions of the desert contained very few colonies of any kind.

Table I contrasts the percentages of the various genera as obtained by the slide method and the plate method. The reversed relationship of *Alternaria* and *Hormodendrum* is no doubt accounted for, in part, by the fact that many individual *Hormodendrum* spores were not recognized on the slides and, in part, by the fact that rusts and smuts do not figure in the plate count percentages. The discrepancies for such genera as *Stemphyllium* and *Helminthosporium* are not so easily accounted for but probably are due to the fact that many spores are nonviable, at least on the medium used.

In Table II the total number of colonies of each genus found on the plates at each of the four stations during 1941 are given. The genera can be divided into five groups with respect to the numbers found at each of the four stations: (1) Those which occur in increasing frequency as one proceeds inland from the beach to the mountains: *Hormodendrum*, sterile mycelia, and *Stamphyllium* (also the total counts); (2) those which are found in increasing numbers as one proceeds inland, except that they fall off at Alpine: *Alternaria, Macrosporium, Botrytis, Epicoccum, Pleospora, Helminthosporium* and *Rhizopus;* (3) those which occur in diminishing frequency as one proceeds inland: *Penicillium, Chaetomium,* and *Plinozythia;* (4) those which behave as the preceding group except for an increase at Alpine: yeasts and *Cephalosporium;* and (5) irregular: *Sporotrichum, Aspergillus, Pringshemia, Fusarium, Monilia,* and *Mucor.*

Of special interest are those spores of diminishing incidence from coast to mountains, particularly *Penicillium.* It may be that this phenomenon is due to the fact that these thrive best in a damp, cool environment, as is known to be true of *Penicillium.*

Sensitization to Fungi.—Table III shows the percentage of allergic patients in this area who reacted to the various genera of fungi. When possible, the reactions to our own extracts were contrasted with the average of the reactions to three commercial extracts. It will be noted that the two most common genera give significantly greater numbers of reactions to the strains of local origin than to the commercial extracts. It is

TABLE III

PERCENTAGE OF ALLERGIC PATIENTS IN SAN DIEGO WHO REACT TO THE VARIOUS INDIVIDUAL GENERA OF FUNGI

(Scratch Method)

	SAN DIEGO EXTRACT	OTHER EXTRACTS (AVERAGE)		SAN DIEGO EXTRACT	OTHER EXTRACTS (AVERAGE)
Hormodendrum	13	7	Aspergillus	4	5
Alternaria	18	12	Pringshaemia	15	
Sterile mycelia	0		Stemphyllium	19	
Penicillium	4	6	Helminthosporium	9	8
Sporotrichum	10		Fusarium		5
Macrosporium	14		Rhizopus	1	
Botrytis	9		Rusts		7
Epicoccum	8		Smuts		3
Pleospora	5		Torula		4
Chaetomium	5	5	Yeasts		6

TABLE IV

COMPARISON OF SKIN TEST REACTIONS TO MOLDS AND POLLENS IN CHILDREN AND ADULTS

(Scratch Method)

	NUMBER TESTED	REACTIONS		
		NEGATIVE (%)	1 PLUS (%)	2 TO 4 PLUS (%)
Molds				
Children	36	39.0	36.0	25.0
Adults	117	74.3	18.8	6.8
Pollens				
Children	35	25.7	48.8	25.7
Adults	114	36.0	34.0	30.0

believed that this difference is due to the fact that we were testing with the particular strains to which the patients had been exposed rather than to any superiority of the extracting method. This belief is supported by the fact that the species within these genera which occurred in greater frequency gave the larger number of reactions.

Table IV shows a comparison of the skin reactions of children and adults to molds and pollens. It will be noted that the number of children sensitive to molds greatly exceeds the number of adults, particularly the number of those strongly sensitive. This fact has been observed by several other authors.[11, 12, 13] Chobot et al.[14] found the reverse to be true for all genera except *Alternaria*, and, for this genus, the percentages were equal. None of the other authors has shown the pollen reactions of the same group. No obvious explanation of this phenomenon, as reported by the majority of observers, suggests itself. It might be said, as a corollary, that mold sensitivity is one of the few disorders which the child really tends to "outgrow."

Protein Content and Rate of Solution.—Even the most accurate knowledge concerning the number of fungus spores in the air leaves still unanswered the question as to the amount of allergen to which the patient is exposed. This amount will depend, first, on the percentage of allergen contained in the spores, and, second, on the rate of solubility of the allergenic component. Pratt and Crossman[15] were able to separate the spores and mycelia of a strain of *Alternaria tenuis* and found that the

TABLE V

NITROGEN CONTENT OF MOLD EXTRACTS

GENUS	STRENGTH OF EXTRACT (%)	TOTAL NITROGEN (MG./C.C.)	PROTEIN NITROGEN (MG./C.C.)	PROTEIN IN PELLICLE (%)	RATE OF SOLUTION
Hormodendrum	10	0.21	0.11	0.7	++
Alternaria	10	0.67	0.27	1.7	+++
Sterile mycelia	5	0.40			+
Penicillium	10	0.27	0.14	0.9	+
Macrosporium	10	0.31	0.16	1.0	+++
Sporotrichum	5	0.17	0.01	0.1	+
Botrytis	10	0.32	0.12	0.7	+
Epicoccum	5	0.12	0.08	1.0	+
Pleospora	10	0.17	0.04	0.2	++
Chaetomium	10	0.20	0.05	0.3	++
Aspergillus	5	0.14	0.10	1.2	+
Helminthosporium	10	0.77			+++
Ambrosia trifida	10	1.60	0.38	2.4	++++
Ambrosia trifida	5	0.77	0.21	1.3	

spores contained at least ten times as much allergen as the mycelia and that at least 95 per cent of the activity resided in the protein. It is, unfortunately, difficult to accumulate enough spores to determine the amount of protein present. For some species it would seem to be well-nigh impossible. Various colonies on the same medium as well as colonies grown under different circumstances contain varying amounts of spores. It is realized, therefore, that nitrogen analyses of extracts made from the whole pellicle do not give an accurate picture. However, for what they are worth, the content of total nitrogen and protein nitrogen for the most common molds found in our survey are given in Table V. In this table a "10 per cent" extract is one containing the soluble portion of 10 Gm. of dry pellicle in 100 c.c. of solvent. The total nitrogen and protein nitrogen values for a "10 per cent" and a "5 per cent" giant ragweed extract are given for comparison. It will be seen that the values for all of the mold extracts listed are less than the corresponding values for the ragweed extracts.

The amount of allergen absorbed by the patient depends not only on the amount present but also on its rate of solution. Particles containing slowly soluble allergens may be washed away by the nasal and conjunctival secretions before complete solution occurs. In the last column of Table V are comparative estimates of the rate with which the well-dried mats of the various molds listed take up water when ground in a mortar. Here again, it would be preferable to deal with spores only, and it would be much more accurate to determine the amount of protein present in the extract after increasing periods of contact of the solvent with the spores. More pressing problems have so far prevented investigation of the subject in this manner. It may be said that in no instance did the mold take up water as readily as do pollens and, when observed under the microscope, *Helminthosporium* spores were the only ones to swell visibly as do pollens when water is added.

TABLE VI

SIZE, SHAPE, AND APPROXIMATE VOLUME OF FUNGI SPORES

(Comparison With Three Representative Pollen Grains)

GENUS		AVERAGE SIZE (IN MICRONS)	SHAPE	APPROXIMATE VOLUME (IN CUBIC MICRONS)
Hormodendrum	No. 1	2.7 by 3	Prolate spheroid	11
	No. 2	8 by 16	Prolate spheroid	540
	No. 3	3 by 5	Prolate spheroid	24
Alternaria		11 by 22.5	Ovate	1,000
Penicillium	No. 1	3	Sphere	14
	No. 2	3.6	Sphere	24
Macrosporium		16.8 by 26	Cylinder with hemispheric ends	3,500
Sporotrichum	No. 1	2.6 by 6	Prolate spheroid	23
	No. 2	7.5	Sphere	270
Botrytis		7.7 by 9.6	Prolate spheroid	300
Aspergillus		3.6	Sphere	24
Stemphyllium		12.7 by 15.4	Cylinder with hemispheric ends	1,300
Helminthosporium		11.8 by 33	Cylinder	3,700
Rhizopus		7.8 by 12.7	Lentil-shaped	200
Rust		21 by 28	Ovate	11,000
Corn smut		5.2	Sphere	73
Yeast		4	Sphere	33
Ambrosia elatior		18	Sphere	3,100
Zea mays		90	Sphere	450,000
Avena fatua		53	Sphere	62,000

Size and Shape of Mold Spores.—There is marked variation in size and shape among mold spores. Table VI gives these data as well as the calculated approximate volume for the various spores found in our survey. The question of the conversion of gravity counts to the volumetric incidence of atmospheric allergens has been ably and painstakingly studied by Durham.[16-18] It is not the purpose of this article to contribute to this complicated subject. However, some comment seems appropriate in order to justify inclusion of the data contained in Table VI, particularly inasmuch as Durham[16] has stated that corrections for variations in velocity of fall may introduce more errors than we seek to correct, due to the varying mass of allergen present in spores of different size.

Let us consider the various corrections now known to be necessary in order to estimate the mass of allergen in a unit volume of air from gravity counts:

1. Volume of the particle ($\frac{4}{3}\ \pi\ r^3$ = volume of a sphere).
2. Density of the particle (d_1) (to convert volume to mass).
3. Rate of fall. The number of particles in a unit volume of air is inversely proportional to the rate of fall, which, for spheres, may be calculated by Stokes' law:

   $$V = \frac{2g\ r^2\ (d_1 - d_2)}{9\ K}$$ where

   V = rate of fall

   g = acceleration of gravity (980 cm. per second)
   r = radius
   d_1 = density of the sphere
   d_2 = density of the medium (air)
   K = coefficient of viscosity of air.
4. Shape and other characteristics (spicules, wings, etc.).
5. Tendency to clump.
6. Impingement (due to nonhorizontal air currents, deflection currents, and eddies).
7. The percentage of the total mass of the particle which the allergenic substance represents.

In addition, the amount of allergen absorbed by the patient will depend upon: (a) whether more allergen is absorbed from multiple small particles than from an equivalent large particle; and (b) the direction and velocity of any movement of the patient with respect to the wind.

It will be seen from corrections 1 and 3, that when Stokes' formula is inverted the r^2 cancels the r^3 in the formula for the volume of a sphere, leaving r. Likewise, from corrections 2 and 3, d_1 (density) cancels out. Hence, on theoretical grounds, at least, corrections 1, 2, and 3 may be summed up by saying that the amount of allergen present in a unit volume of air is directly proportional to the radii (or diameters if preferred) of the particles found on the gravity slides (or plates). Due to irregularities of shape and surface characteristics of mold spores, this determination will be much more accurate when we know the actual experimental rates of fall. If experimental values for rates of fall are used, the density correction (2) will need to be applied. Durham's research shows that the factor of impingement, unfortunately, is the

greatest variable of all. Although there is no way of correcting accurately for this factor in gravity counts already made, even when the direction and velocity of the wind are known it should be possible to devise some type of shelter for gravity slides which would insure accurate air sampling and yet shield the slide from unpredictable air currents. If that can be done, we should be able, with the correction factors listed above, to convert gravity counts to volumetric incidence with a reasonable degree of accuracy.

DISCUSSION

By a simple calculation, too obvious to require description, it may be seen that the plate counts herein reported may be converted to figures equivalent to the slide counts by multiplying by the factor, 6.5. Such equivalents cannot be accepted as accurate, however, unless we can be sure that a twenty-minute exposure of a 90-mm. plate gives us an accurate sample of the mold spore content of the air for the day. Obviously this is seldom the case. However, there should be a constant ratio between a large number of plate counts and a large number of corresponding slide counts. With this conversion, the plate count totals for one year compare with the slide count totals for the same period as follows:

	Hormodendrum	Alternaria	Macrosporium	Helminthosporium	Stemphyllium	Rust	Smut
Slide counts	7,380	3,913	460	490	118	4,776	487
Equivalent plate counts	8,872	3,280	754	136	117	----	---

The excess of the slide counts for *Helminthosporium* over equivalent plate counts probably means that many of the spores of this genus are nonviable on Sabouraud's medium. We cannot explain the discrepancy for *Macrosporium* unless there is development of colonies from fragmented spores or from mycelia.

A comparison with counts obtained elsewhere should be of interest. If we convert our slide counts to counts for areas equal to those used by Durham,[4] namely 1.8 sq. cm., we obtain the following comparative figures:

	San Diego	Chicago	Los Angeles	New Orleans	Seattle	St. Louis	New York
Alternaria	1,130	3,700	1,000	290	28	14,000	560
Hormodendrum	2,130	5,700	1,800	650	600	14,000	1,600

Total daily plate counts for one year compare with those obtained by Bernstein and Feinberg[8] in Chicago, after correcting for the difference in length of exposure, as follows:

	Hormodendrum	Alternaria	Penicillium	Macrosporium	Sporotrichum	Aspergillis	Monilia	Actinomyces	Epicoccum
San Diego	1,991	542	368	278	277	41	12	0	101
Chicago	2,934	2,134	734	0	0	266	220	73	0

SUMMARY

1. The incidence of air-borne fungi in San Diego, California, and vicinity, has been studied over a period of three years by both the gravity slide method and the culture plate method.

2. One hundred thirty-one distinct species, comprising twenty-seven known genera, were isolated. Genera found to be of major importance

include *Hormodendrum, Alternaria,* yeasts, *Penicillium, Macrosporium, Sporotrichum,* and *Helminthosporium.* Those of lesser importance include *Botrytis, Epicoccum, Pleospora, Chaetomium, Aspergillus, Stemphyllium,* and *Pringshemia.*

3. Certain genera occurred with increasing frequency from the beach inland; with others, the reverse was true; and with still others, the distribution was erratic.

4. In this area, the number of children sensitive to molds was found to exceed greatly the number of adults, whereas there was no marked difference in the two groups with respect to pollens.

5. The amount of protein in extracts of the more important genera was determined, and the comparative rate of solution of each was estimated.

6. The approximate size and shape of the spores of the more common fungi found were determined. The bearing of these data on the significance of slide counts and plate counts with respect to the amount of allergen per unit volume of air is discussed.

Each doubtful or unknown colony found in this study was submitted to Prof. O. A. Plunkett, of the Department of Botany of the University of California at Los Angeles, for verification or identification. We wish gratefully to acknowledge his generous assistance and counsel without which this study would have been impossible.

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DEPLETION IN ASTHMA*†

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LAST winter I saw a lawyer, aged 52 years, who had had asthma for nearly two years. His symptoms were severe; he had traveled to various resorts and had seen many doctors in the hope of relief. He had been skin tested and dieted; he had lost most of his strength and about 40 pounds in weight. He was debilitated; he was depleted of body weight and strength.

Treatment given this man was based upon his general condition rather than upon his asthma, and it led to results which, for a time at least, were gratifying. Since then other patients have been found to have a similar debility which, from the practical point of view, was more important than the asthma. In a number of these, gains in weight up to 40 pounds in a year have been accompanied by a degree of improvement which was almost proportional to the weight gain.

There is nothing new in the consideration of the general health in chronic disease, and there is no indication that the debility in asthma is any different from the debility which might lead to attacks of peptic ulcer or arthritis. It is, however, time to call attention to it because so little is said or written about debility in connection with asthma, and in the busy routine the interest is usually more in the asthma than it is in the man or woman who is in trouble and who may get into more trouble when it is so easy to make the treatment worse than the disease.

There is a group of patients consisting mostly of children and young adults who have asthma in isolated attacks, each attack following a new cold. Between attacks these patients are usually perfectly well and show no evidence of allergy or of asthma. The attacks are usually precipitated by new head colds; they may be precipitated by other events, that is, by the excitement of a party or a journey, by simple fatigue brought on by too much exercise, or by late nights even when the patient is still living at home and in the same environment including sleeping in the same bed. In each case, the circumstances of the attack suggest that something happens to "lower the threshold" and allow a slight subclinical degree of allergy to express itself.

Most of the patients in this group have a positive family history of allergy. Many of them have positive skin tests, and quite often the test is helpful in indicating what the offending dust or food material might be. Some of them, however, do not have positive skin tests, and one is left with the doubt as to whether there is an allergy to a dust or food "below the high threshold," as it were, or whether the patient is sensitive to some product of bacterial growth and has a true bacterial allergy; this last diagnosis is very hard to substantiate.

In these cases of "asthmatic bronchitis," the treatment has at least two parts. The one is to remove all possible offending allergens, such as animals, kapok, cotton dust, or feathers, as may be indicated by

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the history and/or by the positive skin tests, and so to establish the principles of "allergic cleanliness." The other part is to do everything possible to improve the health of the patient and especially to protect them against new infections and so to raise the threshold over which his allergy may enter. Improvement of the general hygiene by regulating the time and the quality of meals and daily activities and by instituting adequate periods of rest as well as of fresh air and exercise outdoors is important as also are extra vitamins and vaccines in most of the cases. Such treatment is often satisfactory, and this fact confirms the conception that the asthma was precipitated by a depletion of some factor not yet defined but which could be restored by proper treatment including rest and good feeding.

Another group of cases is more important and not so easy to deal with. In times past I[1] have described "intrinsic asthma" as a disease which comes on quite suddenly and often without obvious cause in an otherwise healthy person over 40 years of age. Skin tests are usually negative, or, at least, if positive, the particular skin test finding cannot be correlated with the history to make a sensible explanation of the trouble. The majority of these patients are in poor general condition; they are thin, tired, and harassed and apprehensive about their trouble.

"Depletion" in asthma may be primary or secondary. It may become manifest before the start of the asthma, and, in this case, one obtains the story of some disease like pneumonia or an operation shortly before the asthma first appeared. Emotional disturbances may precede the asthma and, if they are severe and are complicated by loss of appetite and loss of weight and strength, it is understandable that they could cause depletion. Chronic fatigue dependent upon a hectic life with irregular meals, with almost no rest periods, and with little if any outdoor air has appeared to be a sufficient basis for the start of asthma in a few cases. That is to say, there are many cases in which depletion by itself appears to be a reasonable explanation of the cause of asthma.

On the other hand, "depletion" may be secondary to the asthma, and it is quite obvious that, once asthma from any cause is well established, the general health of the patient falls off, and this in itself makes the asthma worse, just as the presence of severe asthma makes recovery of the general health hard to bring about; a vicious circle is established quite easily. The distinction between primary and secondary depletion is not important, at least from any practical or therapeutic point of view. It is important, however, to recognize that debility may exist and that the treatment of the asthma may not be nearly so important as the treatment of the patient as a whole.

The nature of the depletion is so far unknown. Whether the debility that leads to the isolated attacks of "asthmatic bronchitis" and appears to be a temporary disturbance is the same as the debility which occurs in intrinsic asthma and is so much more persistent will be uncertain until more is known about it. For the moment, it is assumed that the nature is the same in both conditions although varying in degree. It is important to note that nervous and emotional factors and even chronic fatigue may be as active as new infections or as other intercurrent diseases in starting the trouble.

The fact that patients may recover indicates that the debility depends upon a functional rather than upon an organic or pathologic basis. It

may develop quite suddenly in a person who has previously lived many years in good health. Sometimes he or she gives a story of having had asthma for a few years in early life, and so one has to consider the present illness as a sort of conditioned reflex dependent upon the past. In most cases, however, there is no such story.

There are several theories to explain depletion. One of these patients and I were fortunate to have Dr. Fuller Albright see him in consultation. Dr. Albright pointed out that the man had suffered repeated insults to his system and so might be compared with animals which had been exposed to repeated trauma until they were in the resistant or counter-shock stage of the "alarm reaction" as described by Selye and his co-workers.[2] Dr. Albright[3] found that this man excreted in the urine only 5.5 mg. of 17-ketosteroids in one day in place of the normal 15 mg., and he pointed out the probability that the patient suffered from a marked disturbance in the function of the adrenal cortex.

The theory is that, when the body suffers repeated or continued injury, the adrenal cortex hypertrophies, and the "S" hormone, which is concerned with the mobilization of sugar, is produced in excess; the body tissues (protein) are broken down at a rapid rate, and the patient goes into a state of negative nitrogen balance. At the same time the "N" hormone, which is concerned with the building of new tissue, is produced in less than normal quantity, and so replacement of new tissue is not made. The excretion of 17-ketosteroids in the urine is an index of the "N" hormone production, and in this case it was much less than normal.

Meantime, one must recall that injuries such as operations (and, incidentally, they include sinus operations), as well as severe infections, and, in a few cases, physical shock as from a stroke of lightening or emotional shock as from a house on fire, can each and all make the asthma better at least for a short time. This, however, is not incompatible with Selye's theory because one can assume that immediately after an acute injury, that is during the "alarm" proper, the hormones of the adrenal cortex (the "N" as well as the "S" hormones) are squeezed out in excess in the same way that the hormone of the medulla is also squeezed out as Cannon[4] showed some years ago. The relation between adrenocortical changes and asthma may be close, and further results of experiments in Selye's laboratory must be studied carefully. It is possible that other theories concerned with vitamin deficiencies and disturbances of vitamin absorption or vitamin utilization may prove to be even more attractive, but so far there is no evidence to support them.

The treatment of the depletion in these patients has nothing to do with allergy. First of all, the patient must be reassured that, although his lungs may be "stretched" with emphysema and although he has evidence of bronchitis and sinusitis, he is still capable of improvement. While in the hospital such patients do improve so that they may be found at times sitting in bed or in a chair breathing easily, and the fact can be demonstrated as evidence that the function of the heart and lungs is quite capable of becoming sufficient for a quite existence. It should be emphasized to them that they do not have heart disease, or tuberculosis, or even a tumor in the chest. Second, every effort must be made to restore the good condition and that means good food and plenty of it. A full well-rounded diet should be prescribed. Testosterone

propionate acts as a stimulus or perhaps as a replacement of the "N" hormone, and in the one case, Dr. Albright suggested that it be given in doses of 25 mg. intramuscularly every other day for a short time and at longer intervals later. It should be added here that since then testosterone has been given to other patients but without striking benefit. Whether this lack of effect can be taken as argument against the theory is doubtful. This one patient, however, improved considerably so that in the next few months he gained more than 8 pounds in weight and his asthma became much easier to control; he was no longer confined to a bed-and-chair existence, and he was delighted to find that he could go out of doors again and even see his office once more. It was, indeed, unfortunate that six months later he died in a sudden and severe attack of asthma; the first real attack which he had had since the new treatment was begun.

Other patients have followed a similar course. A schoolteacher, aged 58 years, was likewise thin and debilitated—worn down by severe asthma—but treatment was directed toward the improvement of his general health; this was done without the administration of testosterone propionate. The response was very satisfactory. Recently, he was seen again and, in the two years since the first visit, this man has gained 15 pounds in weight and his asthma is almost nonexistent. Let me add, parenthetically, that he is living in the same place now as he was two years ago; that the dusts in his environment are the same now as they were then; that he is eating every kind of food without restriction; and that he has not been "desensitized" to anything. One cannot attribute his great improvement to any element of allergy. There are other patients in this same category and, whereas no figures and percentages can be presented at this time, nevertheless there is no doubt but that the group is of substantial size.

Depletion is important in asthma. The loss of weight and strength is often obvious, and, unless attention is paid to the condition of the patient as a whole, the treatment of the asthma will not be effective. Since the depletion can often be restored by simple improvements in the daily routine with good nursing, rest, good food, and perhaps sunshine, it is fair to assume that the asthma had been aggravated by the loss of some "resistance factor." Nervous and psychic elements are also aggravated by depletion, but they lose their importance when the general health is restored. It often happens that the patient with asthma needs treatment more on the basis of sound general medical practice than on the basis of allergy. In this way, the results of his care are often gratifying.

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Original Articles

VITAMIN C IN HAY FEVER: THERAPY AND BLOOD LEVELS*

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IN THE last two years, and more particularly in the past year, considerable interest has been aroused in the minds of the laity and the profession concerning the use of vitamin C for the relief of hay fever and other allergic conditions. This interest and resultant widespread self-administration of such therapy by numerous sufferers has been engendered largely by the extensive publicity given by newspapers, magazines, and the radio to the paper of Holmes and Alexander,[1] published in 1942. These authors thought that in the fact that histamine destroys vitamin C in the presence of oxygen was to be found an explanation of the low urinary C excretion in hay fever sufferers. Accordingly, they administered vitamin C in amounts varying from 100 to 500 mg. daily and claimed benefit in the majority. Those who took 500 mg. were benefited in two to four days, and occasionally immediately. Hebald,[2] however, administering 500 mg. doses of vitamin C to ten hay fever patients, failed to obtain the results claimed by the previous authors. The claim for the influence of vitamin C therapy in manifestations of hypersensitiveness is not new. Favorable effects have been claimed for the use of vitamin C in anaphylactic shock, sensitivity to histamine, tuberculin, and arsenicals, as well as beneficial results in urticaria, serum sickness, food allergy, and asthma.[3] On the other hand, many workers investigating similar problems report no beneficial effects from vitamin C.[4]

Before reporting our experiences with vitamin C in hay fever it is well to call attention again to the inherent difficulties in evaluating results of hay fever therapy. The severity of hay fever symptoms in the individual depends chiefly on the concentration of pollen in the air. The atmospheric pollen content varies geographically, seasonally, and daily. Furthermore, each individual's response is different, and any evaluation of an individual's results must take into consideration his behavior in past seasons. The analysis is further complicated by the fact that factors other than pollen, such as cold and rain, may be responsible for aggravation of symptoms in some hay fever sufferers during the pollen season. And, not to be ignored, is the fact that psychic suggestion, such as placebo therapy,[5] has been known to be responsible for a fair percentage of claimed improvement in hay fever.

Failure to employ the above considerations in the evaluation of hay fever treatment has been the cause of a large number of new, but short-

The Vitamin C was provided by the Abbott Laboratories.

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lived, therapeutic methods. The paper of Holmes and Alexander, although mentioning pollen counts, does not show evidence that all the proper criteria for such evaluation had been employed.

Although we had previously administered vitamin C in allergic conditions from time to time, the present report is based on a group of forty-three hay fever patients who received vitamin C therapy during the 1944 ragweed season. Since it was difficult to obtain a large number of new hay fever patients for such therapy, our series comprised the following types of patients: (1) Those without any pollen treatment; (2) those who had received so little pollen treatment that effective results were not to be expected; and (3) those who, in spite of fair to adequate pollen treatment, had sufficient hay fever to justify other therapeutic attempts. A total daily dose of 500 mg. of ascorbic acid (in addition to the natural food content) was administered to each of these patients,

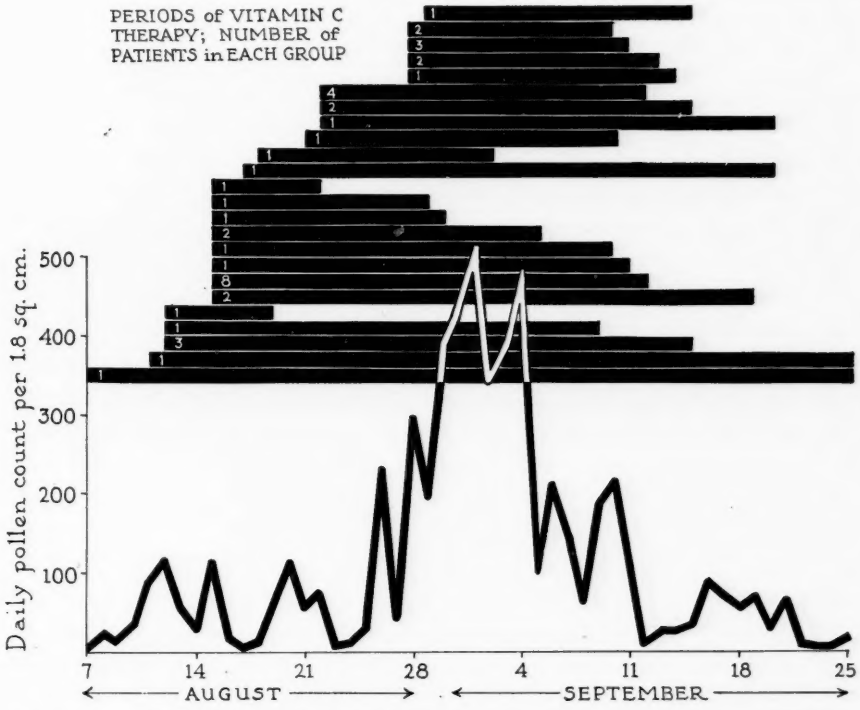

Fig. 1.—Pollen curve for the 1944 fall hay fever season in Chicago. The horizontal lines indicate the dates during which patients received vitamin C therapy, and the numbers at the end of each line indicate the number of patients receiving this therapy during the particular period. (The figures were obtained through the courtesy of O. C. Durham, chief botanist of Abbott Laboratories.)

usually 300 mg. in the morning and 200 mg. in the evening. In one case 1,000 mg. were given daily. The series comprised both children and adults, some with hay fever alone and some with asthma. The patient reported weekly or semiweekly for observation and additional supply of the tablets, and was required to keep daily notes of his symptoms on a card which was turned in at each visit. The length and period of administration of the therapy varied, but most patients began taking their tablets by August 15 and continued to take them for periods varying from two to six weeks. In only two instances was the therapy confined to a period of one week.

TABLE I

POLLEN TREATMENT	NUMBER OF PATIENTS	NOT IMPROVED	IMPROVED
None	11	10	1
Slight	20	19	1
Treated	12	11	1
Total	43	40	3

The therapeutic results were analyzed for each individual, and the evaluation made on a comparison with symptoms in past seasons, with symptoms during parts of the 1944 season, and with many other hay fever patients not receiving vitamin C therapy. The individual patients were divided into three groups, as to pollen treatment. Table I is a summary of the results.

It is apparent that the preponderant percentage of all three groups failed to receive benefit from vitamin C therapy. The claim for improvement in at least one of the improved cases is open to doubt because of the following experience: Following a period of reported improvement the patient was asked to omit one morning dose of the tablets as a condition for blood analysis. That morning she had an attack of hay fever. After a blood sample was taken she was given placebo tablets of the same size and taste as ascorbic acid. She reported later that her symptoms immediately disappeared, and that she remained well while taking these tablets. On her next appearance for blood examination she again had a morning recurrence because she omitted her morning dose of placebo tablets. It is also interesting to note that in no instance was there any claimed improvement in the asthmatic symptoms.

Criticism may be advanced that our series of cases was somewhat selected. This is partially true. The twenty partially treated patients had so little treatment that they may be considered essentially as untreated cases. The twelve cases having a fair amount of pollen treatment and still having remaining symptoms are, in a sense, selected. It is quite apparent, however, that this group illustrates that vitamin C therapy does not even constitute an adjunct in those treated with pollen extracts and having a residue of hay fever symptoms. The pollen graph of 1944, although having its own particular peculiarities, indicates a total amount of pollen of about the average of a number of seasons in Chicago.[6] It is worthy of note, however, that, up to August 26, this 1944 season was unusually mild—a fact which may be the cause of erroneous therapeutic impressions in the minds of the public and inexperienced physicians.

VITAMIN C BLOOD LEVELS

Vitamin C blood studies were made during the season on hay fever patients with and without vitamin C therapy. Since the level in the blood presents a close correlation to the previous dietary intake, it provides a satisfactory method of determining the vitamin C nutrition of the individual at any given time.[7] While the content of the white cell-platelet layer of centrifuged blood may indicate a more accurate index in scorbutic states,[8] any value obtained in the blood plasma is indicative of a positive vitamin C economy, and suitable for determinations in this problem.

TABLE II

GROUP OF RAGWEED HAY FEVER PATIENTS WHO RECEIVED NO SUPPLEMENTS OF VITAMIN C TO THEIR USUAL DIETS

PATIENT	SYMPTOMS	POLLEN TREATMENT IN 1944	BLOOD VITAMIN C	
			DATE	MG. PER 100 C.C.
J. C.	HF	Treated	9/8	0.73
E. S.	HF & A	None	9/12	0.98
J. B.	HF	Slight	9/5	0.75
R. V.	HF & A	Treated	9/12	0.78
Z. S.	HF & A	Slight	9/12	0.76
N. H.	HF & A	Treated	9/5	1.12
F. O.	HF & A	Slight	9/12	0.98
W. J.	HF	None	9/12	0.96
V. B.	HF & A	None	9/12	0.62
C. H.	HF & A	Slight	9/5	1.06
M. R.	HF & A	Treated	9/12	1.20
W. R.	HF & A	Treated	9/5	1.12
J. R.	HF & A	Treated	9/5	0.93
J. U.	HF	Slight	9/12	0.62

HF = hay fever.
A = asthma.

Table II represents a group of eight male and six female ragweed hay fever patients, whose ages range from 6 to 78 years, and who received no vitamin C supplement to their usual diets. All were suffering from active symptoms of hay fever and were instructed to omit citrus fruits from the diet on the morning blood determinations were to be made. The average plasma level for this group was 0.89 mg. per 100 c.c. of blood.

Table III represents six male and twelve female patients, ranging in age from 7 to 69 years, selected from the group of ragweed hay fever patients who received vitamin C. Nine of the group considered in the present study had seasonal asthma in addition to hay fever. The status of these patients as to preseasonal pollen therapy during 1944 may be summarized as follows: one group received no pollen treatment; a second received so little as to be considered inadequate; and a third, despite adequate treatment with pollen, had sufficient residue of symptoms to justify other therapy. Administration of vitamin C was started during the season, after symptoms developed. Blood determinations were made from seven to twenty-eight days after treatment began. Instructions were given to omit the morning dose, as well as citrus fruits from the diet, on the days blood determinations were to be made. An analysis of the findings indicates that while there was some variation for different individuals, and for the same individuals at different times, the average plasma level was 1.28 mg. per 100 c.c. of blood.

The estimated human requirements of vitamin C in the diet vary according to different investigators. For the most part, it is generally agreed that daily intakes for barely adequate consumption are 20 mg. for infants; 40 mg. for children; and 50 to 60 mg. for adults. The average normal level of vitamin C in the blood plasma ranges between 0.6 mg. and 1.5 to 2 mg. per 100 c.c. of blood, depending on the daily intake in the diet.[9] The renal threshold of vitamin C varies widely with the individual, and accounts for the variations in levels of patients receiving saturation doses. The average renal threshold lies between

TABLE III

GROUP OF PATIENTS WHO RECEIVED 500 MG. OF VITAMIN C DAILY IN ADDITION TO THEIR USUAL DIETS

PATIENT	SYMPTOMS	POLLEN TREATMENT IN 1944	VITAMIN C THERAPY 500 MG. PER DAY		BLOOD VITAMIN C		IMPROVEMENT
			BEGUN	DISCONTINUED	DATE	MG. PER 100 C.C.	
A. F.	HF	Slight	8/22	9/12	9/12	1.27	None
C. W.	HF	None	2/29	9/12	9/5	1.48	None
					9/12	1.50	
M. V.	HF	Slight	8/15	9/12	9/12	1.18	None
G. B.	HF	None	8/15	9/12	8/22	2.11	None
					9/12	1.50	
D. B.	HF	Slight	8/15	9/19	9/5	1.44	None
R. B.	HF	None	8/15	9/19	9/12	0.49	None
O. L.	HF & A	Treated	8/22	9/20	9/8	1.59	None
L. W.	HF & A	Slight	8/22	9/12	9/12	1.43	None
A. H.	HF & A	Treated	8/29	9/12	9/5	0.57	None
E. T.	HF & A	Slight	8/15	9/12	9/5	0.78	None
D. T.	HF & A	Slight	8/15	9/12	9/5	1.26	None
R. H.	HF & A	Treated	8/22	9/12	9/5	0.94	None
					9/12	1.29	
G. C.	HF	Slight	8/15	9/12	9/12	1.43	None
J. H.	HF & A	Slight	8/29	9/15	9/5	0.93	None
G. F.	HF	None	8/29	9/12	9/5	1.43	Slight
					9/12	1.16	
F. S.	HF	Treated	8/15	9/12	9/5	1.98	None
					9/12	1.16	
A. M.	HF & A	Slight	8/15	9/12	9/12	0.98	None
L. H.	HF & A	None	8/29	9/12	9/12	1.05	None

HF = hay fever.
A = asthma.

1.1 and 1.8 mg. per 100 c.c. of blood,[10] and blood saturation is considered approximately 1 mg. per 100 c.c. or above.[11] In our present study, fifteen of the eighteen patients receiving 500 mg. daily in addition to their normal diets, were able to reach values approximating the saturation point. In the case of three patients, who had low values, either a low renal threshold, disturbance in absorption, or possible failure to follow directions may be held accountable. Nevertheless, the average patient was able to utilize the vitamin C in a normal manner.

Holmes and Alexander[1] reported that the average hay fever sufferer excretes 10 mg. of vitamin C in the daily urine, as compared to a normal excretion of 30 to 50 mg. daily, thereby assuming a need for additional vitamin C in the diet. There is some doubt that a low urinary excretion is necessarily indicative of vitamin C deficiency.[12] In our present study, the control group represented in Table II, suffering from active hay fever and, in some cases, asthma showed plasma levels which did not vary from those encountered in normal subjects. Goldsmith and her co-workers,[13] studying a group of patients with asthma, reported an average plasma level of 0.41 mg. as compared to 0.60 mg. per 100 c.c. of blood in a control group. More difficulty was reported in reaching and maintaining saturation levels in the patients with asthma, than in normal subjects. Our group of patients, in general, showed little difficulty in attaining saturation levels on supplementary vitamin C in the diet. The inabilitiy to detect any deficiency of the vitamin C nutrition in seasonal hay fever and asthma patients, is in keeping with the absence of therapeutic results when large amounts of vitamin C are administered in these conditions.

SUMMARY

1. Hay fever patients have a normal blood level of vitamin C.

2. Large doses (500 mg. daily) of vitamin C produce the usual saturation blood levels, but do not change the course of the hay fever or asthma.

We wish to express our appreciation to Mary Jean Hauch for her technical assistance.

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ADDENDUM

Since this manuscript was prepared, Dr. D. L. Engelsher, in a letter to the Editor (J.A.M.A. 126: 318, 1944), reported the treatment of forty-eight hay fever patients with 500 mg. doses of ascorbic acid, without benefit.

INHALANT SENSITIZATION AND SHOCK IN GUINEA PIGS UNDER CONTROLLED ATMOSPHERIC CONDITIONS

III. The Possible Effects of Changing Meteorologic Circumstances; A Four-Year Summary

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CLINICIANS who must treat allergic conditions are well aware of the effects of meteorologic change on their patients. The reasons for these effects are not accurately known. This work is an attempt to analyze several components of weather and their actions on inhalant sensitization and shock in guinea pigs. A natural inhalation method of sensitization and shock which was suggested by Ratner[3, 4] and used by us[1, 2] seemed the ideal one to use in testing weather effects. It was hoped that not only interesting data on the effect of atmospheric conditions would result, but that supplementary physiologic and physical factors influencing sensitization and shock would be suggested.

In our study we set forth data concerning the action on sensitization and shock of low and high barometric pressure, cold dry, cold moist, hot dry, and hot moist air, and air that was comparable to that of the average room. We were particularly interested in the physiologic effects of sudden changes; in experiments where we shifted the guinea pigs from one meteorologic condition to a contrasting one.

Our problems concerned not only the responses of the respiratory membranes to weather change but also the possible effect of meteorologic circumstance on the allergenicity of the particulate matter and its attraction to the membrane.

We realized that the use of an experimental animal such as the guinea pig would not allow us to draw any conclusions which could be exactly applied to man. However, we could control the guinea pigs well and felt that when comparisons with man were made of the relative life span and degree of sensitivity, suggestive conclusions could be drawn.[1, 4, 5]

METHOD

Our methods of sensitization as described more fully in the first report were briefly as follows: Healthy female guinea pigs weighing 190 to 280 grams were used, as no differences in sensitization in this size range had been noted. Several unpublished preliminary experiments conducted on inhalation sensitization in adult guinea pigs revealed that adult pigs (900 to 1,000 grams) could usually be sensitized by the inhalation method, but to a lesser degree and less often than the smaller animal. None of the guinea pigs used during our experiments reached a size above 600 grams. All of the experimental animals were obtained from one source in order to minimize the gross differences in susceptibility to sensitization, particularly since a very potent allergen for guinea pigs was used.

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The animals were sensitized by exposure to dust in air chambers in which the atmosphere or "weather" could be controlled and adjusted to simulate room air, hot dry, hot moist, cold dry, and cold moist air. A separate chamber was used for extremely low or high barometric pressures. The constants we had previously established were maintained.

Horse dander, defatted by ether in a Soxhlet apparatus and then dried, was the allergen used throughout. This dander was sifted and then ground in a ball mill until the particles were below 10 microns in size. The circulation of filtered air through each compartment was regulated to 0.15 cubic feet per minute. Ten puffs of dander, representing approximately 0.1 Gm., were blown into the chamber every five minutes. Barometric pressure in the warm compartment was 3 inches of water above that of room air, while that in the cold compartment was 3 inches of water below that of room air. When warm dry or warm moist air was blown into one compartment and cold dry or cold moist air into the other side, a water nebulizer roughly adjusted the droplets of moisture from 0.6 micron to 45 microns in size, to simulate fog.[6] Elements of a cold or warm front except for the gross barometric change were obtained by shifting the animals from one compartment to the other.[7]

The guinea pigs were generally sensitized by inhalation in one weather condition for a total of seven hours, for one hour each day,

TABLE I

SENSITIZATION AND SHOCK IN ROOM AIR

GROUP NUMBER	TYPE OF EXPERIMENT	NUMBER OF ANIMALS	NUMBER OF ANIMAL SHOCK EXPOSURES	MA	A	AS SA	AD	TOTAL REACTIONS
1	Sensitized for a total of 7 hours in room air over an 8-day period; then after an incubation period of 14 days shocked in room air once every week for 3 times	22	63	3	9	21	4	37
2	Sensitized for 8 hours over an 11-day period and shocked on the twelfth day	11	11	2	2	0	0	4
3	Sensitized for 4 hours over an 8-day period and shocked 3 times in one week	5	15	8	1	1	0	10
4	Sensitized for 8 hours over an 11-day period then shocked for 4 successive days	10	40	8	11	5	0	24
5	Sensitized for 7 hours over an 8-day period then after a 14-day incubation period shocked every week for three times	7	20	5	8	4	1	18
		55	149	26	31	31	5	93 (61%)

Symbols: MA=mild asthma; A=asthma; AS=anaphylactic shock; SA=severe asthma; AD=anaphylactic death.

over an eight-day period. Then, after a fourteen-day incubation period they were re-exposed to the dry horse dander dust in the chamber in any one of the experimental weather conditions. Reactions on shock exposure had been observed so many times in previous experiments that the typical diaphragmatic breathing could be quite accurately symbolized as to degree. At the end of a series of shock exposures, which usually took place every seven days after sensitization, all pigs were injected intrajugularly with 0.5 c.c. of horse dander extract. This last procedure was a final test of the general sensitivity of each animal.[3]

Variables of outdoor weather in San Francisco were obtained for each day of experimentation and for several days before and after.[8] We also kept a record of the humidity and temperature of the laboratory room.

EXPERIMENTAL DATA

Table VI illustrates how we compiled our data and related the outdoor weather change, room air, and experimental chamber weather to

TABLE II

SENSITIZATION AND SHOCK IN HOT DRY AIR

GROUP NUMBER	TYPE OF EXPERIMENT	NUMBER OF ANIMALS	NUMBER OF ANIMAL SHOCK EXPOSURES	MA	A	AS SA	AD	TOTAL REACTIONS	
1	Sensitized for a total of 7 hours over 8 days, then after a 14-day incubation, shocked every 7 days, 3 times	22	57	5	7	23	7	42	
2	Sensitized for 7 hours in hot dry air over an 8-day period then after an incubation period of 14 days shocked in in hot dry air every 4 to 7 days for 3 months	5	55	4	11	26	0	41	
3	Sensitized for 7 hours in hot dry air over an 8-day period, then after an incubation period of 3 days shocked in hot dry air every 3 days to 2 weeks over 2.5 months.	6	42	7	7	14	2	30	
4	Sensitized for 6 hours over 7 days, then shocked once after an 8-day incubation and re-shocked 10 days after that	5	10	0	0	7	0	7	
5	Sensitized for 5 hours over 9 days, then after an 18-day incubation, shocked every 7 days for 8 times	6	28	3	4	14	4	25	
6	Sensitized for 3.5 hours in hot dry air over a 9-day period, then, after an incubation period of 2 days, shocked in hot dry air every 3 days for 6 times	4	22	9	2	8	2	21	
7	Sensitized for 7 hours over 8 days, then, after a 14-day incubation, shocked every 7 days, 3 times	10	30	4	5	9	2	20	
		58	224	32	36	101	17	186	(83%)

the exposure and reactions of the guinea pigs. Rather than depict each experiment in this way much of our data of the last four years is shown in Tables I through V under headings "Room Air," "Hot Dry," "Hot Moist," "Cold Dry," and "Cold Moist Air."

Five experiments are shown in Table I. The animals were sensitized and shocked by inhalation of dry horse dander in atmospheric conditions comparable to those of room air. The temperature of the air varied from 68° to 70° F., and the relative humidity from 55 to 65 per cent. The actual moisture in the air was from 60 to 90 grains per cubic foot, and the vapor pressure varied from 0.40 to 0.61 inches. Fifty-five animals were used and there were 149 exposures. A total of 93 (61 per cent) anaphylactic reactions took place.

Seven experiments are recorded in Table II. All animals were sensitized and shocked by inhalation of dry horse dander in dry hot air. The temperature of the air varied from 94° to 110° F. with relative humidity ranging from 20 to 45 per cent. Vapor pressure was from 0.51 to 0.66 inch, while the actual moisture of the air varied from 80 to 105 grains per cubic foot. Fifty-eight animals were sensitized and 224 shock exposures were made. There were 101 instances of severe expiratory dyspnea and sublethal anaphylactic shock. Seventeen died an anaphylactic death. Reactions total 186 (83 per cent).

TABLE III

SENSITIZATION AND SHOCK IN MODERATELY HOT, MOIST AIR

GROUP NUMBER	TYPE OF EXPERIMENT	NUMBER OF ANIMALS	NUMBER OF ANIMAL SHOCK EXPOSURES	MA	A	AS SA	AD	TOTAL REACTIONS
1	Sensitized for a total of 7 hours over an 8-day period, then, after a 14-day incubation, shocked every 7 days, 3 times	18	49	31	9	8	1	49
2	Sensitized for a total of 6 hours in moderately hot, moist air over a 7-day period; then, after an incubation of 8 days, shocked in hot moist air every 7 days, 4 times	7	28	3	3	19	0	25
3	Sensitized for 7 hours over 8 days, then, after an incubation of 10 days, shocked every 7 days, 4 times	4	16	10	2	3	0	15
4	Sensitized for 7 hours over 8 days, then, after an 8-day incubation, shocked every 7 days, 4 times	6	21	3	2	15	1	21
5	Sensitized for 5 hours over 6 days, then, after a 7-day incubation, shocked every 7 days, 4 times	5	20	2	2	16	0	20
6	Sensitized for 4 hours over 7 days, then continued exposure every days for 4 days, then shocked every 3 to 7 days for 4 times	6	48	6	19	13	0	38
		46	182	55	37	74	2	168 (90%)

Six experiments are shown in Table III. The guinea pigs were sensitized and shocked by inhalation in moderately moist, hot air. The temperature ranged from 89° to 96° F., with relative humidity from 72 to 95 per cent. The actual moisture ranged from 150 grains to somewhat over 150 grains per cubic foot. Vapor pressure varied from 0.9 to 1 inch. Forty-six animals were tested, there were 182 exposures and 168 reactions (90 per cent).

Seven studies are presented in Table IV. The guinea pigs were sensitized and shocked in relatively cold, dry air. Experimental weather temperatures varied from 37° to 43° F. with relative humidity from 45 to 55 per cent. There were 15.5 to 25 grains of actual moisture per cubic foot of air, and from 0.09 to 0.157 inch of vapor pressure. Fifty guinea pigs were used and 169 individual shock exposures made. A total of 120 reactions occurred (70 per cent).

Four experiments are listed in Table V. The experimental chamber contained cold moist air, 100 per cent relative humidity with temperature from 38° to 45° F., and vapor pressure from 0.23 to 0.31 inch. Forty-five animals were used, and 206 shock exposures made. Sixty-two reactions occurred (30 per cent).

The data on the "shift" experiments were too voluminous to condense into tables. We performed ten experiments which were varied and complex as far as types, periods of time, and intervals between exposures

TABLE IV

SENSITIZATION AND SHOCK IN COLD DRY AIR

GROUP NUMBER	TYPE OF EXPERIMENT	NUMBER OF ANIMALS	NUMBER OF ANIMAL SHOCK EXPOSURES	MA	A	AS SA	AD	TOTAL REACTIONS
1	Sensitized for 6 hours in cold dry air over a 7-day period, then, after an 8-day incubation period, shocked in cold dry every 14 days, 2 times	6	12	1	4	1	1	6
2	Sensitized for 7 hours over 7 days then, after a 10-day incubation, shocked every 7 days for 4 times	5	17	0	3	9	1	13
3	Sensitized for 7 hours over 8 days, then, after an 8-day incubation, shocked every 7 days for 4 times	5	20	1	7	11	0	19
4	Sensitized for 5 hours over 6 days, then, after a 7-day incubation, shocked once	5	5	0	4	1	0	5
5	Sensitized for 4 hours over 7 days, then continued exposure for 4 days, then shocked every 3 to 7 days for 4 times	6	48	2	9	15	0	26
6	Sensitized for 7 hours over 8 days, then, after a 14-day incubation, shocked every 7 days for 3 times	11	33	9	12	5	0	26
7	Sensitized for 7 hours over 8 days, then, after a 14-day incubation, shocked every 7 days for 3 times	12	34	8	11	6	1	25
		50	169	21	50	48	3	120 (70%)

were concerned. These variations we believed would simulate the random exposure and preconditioning environment to which man is subjected. In some instances the animals were shifted from one extreme of atmosphere to another during sensitization. In other instances they were sensitized in one particular air condition, and then subjected to the shifting back and forth immediately before or during shock exposures. In these 10 experiments 90 animals were used and 331 animal shock exposures made. There were 45 reactions of mild asthma, 69 of moderate, 158 of severe asthma and anaphylactic shock, and 14 instances of anaphylactic death by inhalation. This is a total of 286 reactions (86 per cent), in spite of the fact that some of the shock exposures were made in cold moist air, a condition where, usually, few reactions occurred.

Our clinical laboratory impressions were substantiated by the statistical data in most instances. However, we plan, in a future article, to analyze further the results of these "shift" experiments. We are preparing a longitudinal life chart for each animal; that is, one similar to that devised by Adolph Meyer for use in psychobiologic studies. In this way we hope to find more exact and various relationships between periods of time, degrees of reaction, and types of meteorologic circumstance.

In Table VI is shown the detail of an experiment where animals were sensitized by exposing them, in immediate sequence, to horse dander dust for ten minutes in hot moist air, then for twenty minutes in cold dry air, and again for ten minutes in hot moist air. Such sensitizing exposures took place over a period of eight days; then, without further incubation, the guinea pigs were shocked. The shock exposures

TABLE V

SENSITIZATION AND SHOCK IN COLD MOIST AIR (100 PER CENT R.H.)

GROUP NUMBER	TYPE OF EXPERIMENT	NUMBER OF ANIMALS	NUMBER OF ANIMAL SHOCK EXPOSURES	MA	A	AS SA	AD	TOTAL REACTIONS
1	Sensitized in cold moist (100% R.H.) air for 7 hours over 8 days, then, after 14 days incubation, shocked every 3 to 4 days for 5 times before any reactions took place, then every 7 days for 3 times	7	56	2	3	0	0	5
2	Sensitized for 5 hours over 9 days, then, after an 18-day incubation, shocked every 7 days for 8 times	6	54	8	8	15	0	31
3	Sensitized for 6.5 hours over 8 days, then, after 14 days incubation, shocked every 7 days for 3 times	13	39	7	5	5	0	17
4	Sensitized for 7 hours over 8 days, then, after 14 days incubation, shocked every 7 days for 3 times	19	57	2	5	2	0	9
		45	206	19	21	22	0	62 (30%)

were accomplished by a preconditioning shift of the animals from ten minutes in hot moist air to twenty minutes in cold dry air without dander; then shocking them in hot moist air (90° to 95° F., and 70 to 90 per cent relative humidity) plus dander. There were 86 individual

TABLE VI

DATA ON SHIFT SENSITIZATION HOT MOIST TO COLD DRY TO HOT MOIST REACTIONS OF ANIMALS

		OUTSIDE WEATHER							ROOM AND CHAMBER WEATHER						NUMBERS														
	Date	Weather Outside	Total Wind	Sun %	Precip Inches	Barometric Pressure Maximum	Temp F Max	Temp F Min	Noon Vap Pressure	Est Weather Change + or - Bar Press & Air Mass Change	Room Temp	Chamber Temp	Room R H	Chamber R H	Grs Moisture Vapor Per Cu Ft Air Chamber	Press Chamber	Exposure Time	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
	Feb 1942																															
17		Sun Warm	149	93	0	29 85	29 75	57	45	256	Bar Press Static Vap Press 0 1 Sl W & W	71	92	52	80	150± 13	10 M																
													40		70	24 5 0 17	20															
													90		80	150± 13	10															
17		Clouds Chill	135	70	0	29 90	29 80	57	47	277	Bar Press Static Vap Press 0 12 Sl W & C	68	92	60	85	150± 1 29	10																
													48		55	27 0 0 19	20															
													92		85	150± 1 29	10															
18		Clouds Sl Warm	124	5	0	30 00	29 90	55	50	287	Bar Press Static Vap Press 0 11 Sl C & C	70	94	60	75	150± 1 13	10																
													44		60	26 0 0 17	20															
													94		75	150± 1 13	10															
19		Fog	110	56	0 3	30 00	29 90	62	48	277	Bar Press Static Vap Press 0 11 Static	72	94	60	80	150± 1 29	30																
20		Sun Warm	106	91	0	29 91	29 70	59	47	228	Bar Press Falling Vap Press 0 12 Static	74	94	50	80	150± 129 C	10																
													48		50	25 0 0 16 C	20															
													92		80	150± 129+ C	10															
21		Rain	220	25	013	29 65	29 45	52	47	310	Bar Press Falling Vap Press 0 08 D & C	71	90	58	85	150± 1 4	10																
													44		48	21 0 0 13	20															
													90		85	150± 1 4	10															
22		Cloudy	140	61	T	29 99	29 85	55	46	247	Bar Press Rising Vap Press 0 09 Static	74	90	48	85	150± 1 4	10																
													46		42	19 0 0 125	20															
													90		85	150± 1 4	10															
24		Rain Sun	205	70	023	29 88	29 70	53	45	247	Bar Press Sl Fall Vap Press 0 12 Wetter	76	92	45	80	150± 1 29+ Sl C	10				A A A

contrast they were performed on the same days, for the same periods of time. Sensitization was accomplished by exposing the animals for a total of seven hours over an eight-day period. After a fourteen-day incubation period they were shocked every seven days, a total of three times. The exposures in low and high barometric pressure were made in a separate chamber so arranged that the air drawn through was dried by alumina. The desired pressure was attained gradually over a ten-minute period before the dander was puffed in. Before removing the animals the pressure was slowly returned to sea level. None of the animals showed any obvious symptoms from the change in pressure itself. One experiment compared reactions of 12 animals sensitized and shocked in low pressure (minus 15 inches of mercury) to 12 sensitized and shocked in room air at sea level. There were 68 per cent reactions in low pressure and 55 per cent in room air. The other experiment compared reactions of 12 animals sensitized and shocked in high pressure (plus 30 inches of mercury) to 12 done in room air at sea level. There were 49 per cent reactions in the high pressure and 61 per cent in room air. More work is planned to determine the many effects of low and high pressure on inhalation sensitization and shock, but we believe that the greater percentage of reactions in low, over those in high, pressure is significant.

Table VII divides the total reaction percentages into five categories: (1) severe reactions in the first shock exposure, (2) totals of all reactions, mild to lethal, in the various experimental weather conditions, (3) severe reactions in all experiments, (4) anaphylactic deaths by inhalation in the various meteorologic conditions, and (5) mild reactions in the "nonshift" experiments.

There were over 350 guinea pigs used, and at least 1,500 animal shock exposures made. It can be noted in Table VII that the least number of reactions occurred in the cold, moist air, while air comparable to room air produced the next to the least number of reactions except when the extremes were counted as in the fourth and fifth categories. On the other hand, the three conditions which produced the greatest number of reactions were the shifts from low pressure to hot dry air; hot moist to cold dry and back to hot moist; and hot dry to low pressure.

The hot, dry air seemed to help produce more severe reactions in the first shock exposure than any other single weather conditions. The hot moist air was conducive to very many reactions under all categories except anaphylactic death, in contrast to the hot dry air in which many anaphylactic deaths but very few mild reactions occurred. The cold dry air appeared to be consistently intermediate under all reaction headings. The significance of the percentages shown in Table VII is decreased in many respects because many types of sensitization and time distributions were used. The same thing can also be said of statistical studies on human patients where the time sequence and other factors of sensitization and shock cannot be controlled even as accurately as with guinea pigs.

For this reason we contrast the percentages in Table VII with those in Table VIII where only experiments comparable in time sequence of sensitization were used, namely; Experiments 1, 2, 6 in room air; 1, 2,

TABLE VII. LIST OF TYPES OF WEATHER CHANGE IN THE ORDER OF ITS EFFECT ON EXPERIMENTAL ASTHMA WHEN THE PERCENTAGE OF REACTIONS IS STUDIED

I ONLY SEVERE REACTIONS ON FIRST EXPOSURE		II ALL REACTIONS MILD TO LETHAL		III SEVERE REACTIONS IN ALL EXPOSURES		IV ANAPHYLACTIC DEATHS BY INHALATION		V MILD REACTIONS	
TYPES OF EXPERIMENTAL WEATHER	ORDER OF FREQUENCY	TYPES OF EXPERIMENTAL WEATHER	ORDER OF FREQUENCY	TYPES OF EXPERIMENTAL WEATHER	ORDER OF FREQUENCY	TYPES OF EXPERIMENTAL WEATHER	ORDER OF FREQUENCY	TYPES OF EXPERIMENTAL WEATHER	ORDER OF FREQUENCY
Low pressure to hot dry	1	Hot moist to cold dry to hot moist	1	Low pressure to hot dry	1	Hot dry to low pressure	1		1
Hot dry	2	Low pressure to hot dry	2	Hot moist to cold dry to hot moist	2		2		2
Hot moist	3	Hot moist	3	Hot dry	3	Hot dry	3	Hot moist	3
Hot moist to cold dry to hot moist	4	Hot dry	4	Hot moist	4	Room air	4	Room air	4
Cold dry	5	Cold dry	5	Cold dry	5	Cold dry	5	Hot dry	5
Room air	6	Room air	6	Room air	6	Hot moist	6	Cold dry	6
Cold moist	7	Cold moist	7	Cold moist	7	Cold moist	7	Cold moist	7

TABLE VIII. LIST OF TYPES OF WEATHER CHANGE IN THE ORDER OF ITS EFFECT ON EXPERIMENTAL ASTHMA WHEN THE PERCENTAGE OF REACTIONS IS STUDIED IN A SELECTED GROUP OF EXPERIMENTS

I ONLY SEVERE REACTIONS IN THE FIRST EXPOSURE		II ALL REACTIONS MILD TO LETHAL		III SEVERE REACTIONS IN ALL EXPOSURES		IV ANAPHYLACTIC DEATHS BY INHALATION		V MILD REACTIONS	
TYPES OF EXPERIMENTAL WEATHER	ORDER OF FREQUENCY	TYPES OF EXPERIMENTAL WEATHER	ORDER OF FREQUENCY	TYPES OF EXPERIMENTAL WEATHER	ORDER OF FREQUENCY	TYPES OF EXPERIMENTAL WEATHER	ORDER OF FREQUENCY	TYPES OF EXPERIMENTAL WEATHER	ORDER OF FREQUENCY
Hot dry	3	Hot moist	3	Hot dry	3	Hot dry	3	Hot moist	3
Hot moist	4	Cold dry	4	Room air	4	Room air	4	Cold dry	4
Cold dry	5	Hot dry	5	Cold dry	5	Cold dry	5	Hot dry	5
Room air	6	Room air	6	Hot moist	6	Hot moist	6	Room air	5
Cold moist	7	Cold moist	7	Cold moist	7	Cold moist	7	Cold moist	6

8, in hot dry air; 1, 2, 4, in hot moist air; 2, 6, 7, in cold dry air; and 4, 5, in cold moist air. Thus, it is readily noted that the hot, dry air helped to produce the more severe reactions; room air, next; and cold dry air, third. Hot moist air was first, and cold dry air consistently second in producing reactions when all types or only mild reactions were considered. Table VIII shows room air more consistent in producing a greater number of severe reactions, but a smaller number of all types, and of mild reactions. The data in Table VIII is used in our discussion and summary.

When we analyzed all of our outside weather data for the four years in relation to its possible effect on the reactions of our experimental animals, we verified the negative findings quoted in a former paper.[1] No correlation was found between the severe reactions of the guinea pigs and variation in weather as shown by the air mass movement[7] coming into San Francisco from the ocean, as, for example, the change from Polar to Tropic Pacific. It may be well to emphasize that, in San Francisco, there is much less gross barometric pressure change than in many cities,[9] although clinically in man the diurnal changes here, from fog to drier air, may be significant in aiding the production of asthmatic attacks.

It is fairly safe to assume that in our experiments most of the meteorologic effect on sensitization and shock depended on the experimental conditions although a few more instances of severe anaphylactic shock occurred when the outdoor barometric pressure was falling, and the vapor pressure rising.

DISCUSSION

Our clinical findings tend to show that there may be a relation between them and certain physiologic regulatory mechanisms stressed by a number of authors.[10-51] If certain weather conditions cause minor changes in animal tissue and particulate matter, the sum total of which is harmful, it is likely that the normal homeostatic rhythm will become unbalanced and clinical symptoms result.[22] For example, in the hot dry air the following harmful conditions probably prevailed: (1) the heat itself, which was harmful to the already excited animals; (2) increased vascularity of the upper respiratory membrane with nasal block and increased eddies of air which caused more allergen particles to contact the membrane; (3) lowered membrane temperature and decreased tissue fluids, which increased the difficulty of the local tissue in handling the allergen; (4) increased viscosity, osmotic pressure, and surface tension of the mucus, and decreased activity of the cilia which prevented the particles from being eliminated physically; and (5) increased chemical and immunologic activity of the antigen, and decreased air layer adsorption on the particle surface, both of which aided the absorption of the allergen.

In contrast to the hot, dry air, the hot, moist air probably produced the following conditions: (1) decreased vascularity of the nasal membrane with free flow of air; (2) fairly normal activity of the cilia and

condition of the mucus. Otherwise the conditions were the same as in the hot dry air.*

Although the largest number of reactions in the single weather conditions occurred in the hot moist air, many were mild, and there were no anaphylactic deaths by inhalation. It is possible that the animals were locally and less generally sensitized because less allergen was absorbed by the membrane, or perhaps it was better eliminated.[52-54]

It is important to note that, with the exception of the hot dry air, more severe reactions and anaphylactic deaths occurred in the room air experiments. These obtained even though the animals were subjected to less weather change when taken from their cages and placed in the chamber containing room air, than they were when subjected to the other experimental weather conditions. The fact that the vapor pressure of our hot dry air and that of the room air were approximately 0.50 inch, may have been of prime importance, in such temperature ranges, in causing the similar statistics. However, there were far more severe reactions on the first shock exposure in hot dry air than in room air.

In the cold dry air the following factors possibly balanced each other and produced the intermediate number of reactions noted: (1) the cold itself, which was less disturbing than heat to the usually excited animals; (2) decreased vascularity of the nasal membrane with free flow of air; (3) increased membrane temperature and tissue fluids, which decreased the difficulty of the local tissue in handling the allergen; (4) increased stress on membranes to heat; (5) less activity of the cilia and increased viscosity of the mucus; and (6) less activity of the particulate matter but more electrostatic charge for adsorption on the membrane. Petersen[22] emphasizes that in quick cold there is a "retreat" into the body, and the body cells are less permeable. This might explain the slower sensitization of the animals in cold, than we found in hot, air.

The reason for the smaller number of reactions in the cold moist air may be that very little allergen was available to the membrane because the fine spray of "fog" (100 per cent relative humidity) which we used probably washed the particles of allergen away. An 80 to 90 per cent relative humidity might have changed our results. In addition to this, the mucus probably was in a good environment for eliminating the particles. The other conditions here were the same as those beneficial ones listed under cold dry air. We were particularly interested in the fact that fewer reactions took place in the cold moist air because the higher incidence of asthma in San Francisco is commonly thought to be, in part, due to the cold fogs.

Spiesman and Arnold[32] and others stress that there are hypersensitive individuals whose reactions to weather change are the converse of those normal reactions described above. It is probable that we developed hypersensitive animals in our experiments, and because of this our results may have varied at times from those one would expect.

*In order to test the effect of high temperatures (118° F. with 100 per cent relative humidity) on animals with increased basal metabolic rates, eighteen guinea pigs were given thyroid extract until the average basal metabolic rate was +20 per cent, and then sensitized in the hot moist air. Six animals died from the heat during sensitization, and all but two of those remaining died from the heat and mild anaphylactic symptoms during the first shock exposure. A limitation of time prevented us from testing similarly conditioned pigs in cold air.

Beyond question, the experiments in which the animals were shifted from one extreme of weather to another produced the most reactions in all categories listed. A theoretical explanation of these results would be too complicated for the scope of this paper. We wish to mention, however, that the guinea pigs were subjected to an "alarm" reaction each time they were shifted, as the time period between each change was not long enough to allow for good adjustment. Petersen and Vaughan[51] recently gave reasons why tissue swelling may be increased when a tropical air mass follows a cold one. Black[24] stressed the decrease in tissue fluids and increase in blood volume which occurs in moderate lowering of the barometric pressure. The gross pressure changes we used must have produced much greater effects. The shift from hot air to low barometric pressure was interesting in relation to the meteorologic changes to which combat aviators are subjected. In the change from sea level to the low barometric pressure it is probable that the guinea pigs were handicapped by the low oxygen tension in addition to the mechanical difficulty of breathing, during asthmatic reactions.

Much work must be done before we can fully understand the effects of weather change on the allergic individual. It is our belief, however, that in the management of such patients an effort should be made to analyze the particular meteorologic changes to which he is subjected.

SUMMARY

1. Statistics are presented of reactions of 350 guinea pigs sensitized and shocked by inhalation of horse dander in various controlled weather conditions. More than 1,500 shock exposures were made.

2. The conditions under which the greatest number and most severe anaphylactic reactions occurred were: (a) shifting from hot dry air to low barometric pressure, (b) shifting from low pressure to hot dry air, and (c) shifting from hot moist to cold dry air without the allergen and back to hot moist with the allergen.

3. The single weather conditions, in the order of the number of severe reactions which occurred in each were: (a) hot dry, (b) room air, (c) cold dry, (d) hot moist, and (e) cold moist air.

4. The single weather conditions, in the order in which the greatest number of all types of reactions occurred were: (a) hot moist, (b) cold dry, (c) hot dry, (d) room air, and (e) cold moist air.

5. The single weather conditions, in the order in which the most severe reactions in the first shock exposure occurred were: (a) hot dry, (b) hot moist, (c) cold dry, (d) room air, and (e) cold moist air.

6. In one well controlled experiment the experimental low pressure condition was conducive to a significantly higher number of reactions than was that of high pressure.

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PROPEPTANS IN THE TREATMENT OF RAGWEED HAY FEVER*

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THE obvious inconveniences of a long course of injections for the victims of hay fever have led to many attempts to achieve therapeutic results by oral administration of pollens in such cases. Iliff and Gay[1] have reviewed the literature on this subject and have presented the impressions gained on eighty-two patients who were given oral treatment in our clinic.

In his recent book, *Allergy,* Urbach[2] reports that he has employed "pollen propeptans" for the last two years with very satisfactory results. This preparation is said to be derived from the individual pollen by digesting the proteins with hydrochloric acid, pepsin, and trypsin. The author claims that therapy with propeptans accomplishes deallergization, in contrast to hyposensitization in parenteral treatment. He believes that this deallergization becomes permanent—in the case of food allergy within one or two weeks—and ultimately leads to loss of specific hypersensitiveness and thus to "cure." The assumption is that administration of small amounts of antigen elicits so-called microshocks which are followed "not only by loss of antibodies owing to satiation, but also by an arrest of antibody production." In guinea pigs "deallergized" by means of oral administration of a great variety of antigens, not only the lungs but also the uterus failed to react to the specific antigen; passive transfer also became impossible in these animals. A booklet[3] prepared by the manufacturers of the propeptans† points out that, in unpublished experiments, guinea pigs sensitized to ragweed pollens were protected against anaphylactic shock by intravenous or oral administration of ragweed pollen propeptan; the intravenous injection of ragweed pollen digest protected against up to five times the lethal dose of a 5 per cent ragweed pollen extract.

In addition to these promising features of pollen propeptan, this preparation is said to have the advantage of being followed by side effects "only very occasionally" in contradistinction to the observations with whole pollens.

We selected a small group of ragweed hay fever patients for treatment with pollen propeptan capsules which were liberally supplied by the manufacturer. (Three patients who were started on treatment are not included in our figures because of their failure to make final reports.) The total duration of the hay fever in these cases varied from six to twenty-one years; the symptoms were strictly seasonal except for three patients who had also spring hay fever. The majority of the patients had no, or inadequate, treatment previously. Three of the patients had parenteral treatment perennially, one had oral treatment in 1941 and 1942 with Panoral, all with only fair results.

Seven of the patients were started on treatment six weeks before onset of the ragweed season; two other groups of two patients each were started four and five weeks, respectively, before onset of the season.

*From the Protein Clinic of the Medicine Dispensary of the Johns Hopkins Hospital.

†Dalare Associates in Philadelphia.

There was no definite relationship between the length of the treatment and the results obtained. Treatment was commenced with one capsule daily containing 60,000 units of giant ragweed and dwarf ragweed in equal parts. The dose was gradually increased up to six capsules representing 360,000 units daily, and this dose was continued from the onset to the end of the season, except for one patient who discontinued treatment on August 26 because of severe side effects, and a second patient who was switched to parenteral treatment upon his request on September 9 because of failure to obtain relief from the preparation. One patient took 480,000 units at times during the season. This patient belonged to the group which had no beneficial result, and she experienced the worst season she ever had.

Side effects were observed in four of the eleven cases, ranging from slight occasional abdominal pain and itching of the skin to nausea, diarrhea, and cramps. No patient had any hay fever symptom as a reaction to the ingestion of the capsules. One patient with pronounced side effects could continue the treatment after reducing the dose and stepping it up again; a second patient discontinued the capsules because of severe abdominal cramps after having experienced minor discomfort and nausea ever since she commenced treatment.

The results of the treatment were as follows: season better than last year, three; symptoms same as last year, three; hay fever worse, five. Of the three patients who thought that they had been helped by the capsules, one had apparently always mild symptoms; the other two had a very bad week at the height of the season but felt that the rest of the season was less severe than usual. As these patients had never had treatment before, a psychological factor might have influenced their estimation of the result. If we keep in mind that, as a whole, the ragweed season of 1944 was more severe than average, we might list these three patients with a better season together with the three patients who believed that their trouble was the same as usual (and not worse in spite of the more severe season), and characterize, therefore, six cases as "improved in some degree." These cases would correspond to the group with fair relief in Iliff and Gay's series. Not a single patient, however, experienced anything approaching satisfactory or complete relief. Of the five patients who stated that they were worse than last year, four had no treatment in the previous season; one had perennial treatment with poor results; and one patient, who had never required treatment before, had to go to the accident room for relief on one occasion.

The passive transfer test was strongly positive in the serial dilution method in nine cases at the end of the treatment period. One patient

TABLE I

REAGIN TITER IN PATIENTS TREATED WITH RAGWEED POLLEN PROPEPTANS

PATIENT	BEFORE TREATMENT	MIDSEASON	AFTER TREATMENT
Fl			1:128
B			1:128
Vl			1:16
Mc All	1:16		1:64
Br	1:4	1:256	
Pr			1:128
Si			1:64
Bea	1:4		1:64
Re	1:128		1:128
Mc Do	1:2		1:64

failed to return for the test, a second was tested in midseason with positive reaction in a dilution of 1:256. The end point in the nine cases was reached with a dilution of 1:64 or 1:128, except for one case with an end point of 1:16. Five patients were tested at the onset and after conclusion of the treatment, with the result that one patient had the same titer both times, while the serum of the others produced positive reactions in much higher dilutions at the end of the treatment period than at the beginning. The patient who was retested in midseason had, likewise, a much higher antigen titer after having taken propeptans for ten weeks (Table I).

Thus we have to state that in our small series of ragweed hay fever patients, only fair results, at best, could be obtained in about one-half of the cases treated with pollen propeptans while the other half of the cases were complete failures. There was not the slightest evidence of "deallergization" if the presence of transferable reagin is taken as an index. Side effects were about as frequent as with other oral preparations.

Up to the writing of this article, no chemical analysis of pollen propeptans has been published as far as we have seen. Two analyses, however, have been given recently of food propeptans (beef and egg). No acid precipitated nitrogen was found in these analyses.[4] In 1934, Urbach and Kitamura[5] stated that the propeptans are free from native "Eiweiss," as tests with 20 per cent sulfosalicylic acid and with 20 per cent trichloracetic acid had negative results. The booklet on propeptan therapy, distributed by the manufacturer, implies that the pollen propeptans do not contain native protein. We tested an aqueous solution of the content of some pollen propeptan capsules obtained from the manufacturer with 20 per cent trichloracetic acid and found a marked precipitation. Incidentally, egg propeptan received from the same source likewise showed a very definite precipitation on addition of 20 per cent trichloracetic acid to an aqueous solution. It seems, therefore, that the question of whether the propeptans are really free from native protein deserves reinvestigation.

SUMMARY

1. Treatment of hay fever patients with ragweed pollen propeptans was a complete failure in five of eleven cases, while six patients had fair relief at best, if we disregard the psychological factor of a new kind of treatment. No case had a good or excellent result. Side effects from light to severe were seen in four of the eleven cases.

2. The antigen titer following treatment was high in the passive transfer test, and it exceeded considerably the titer before the treatment in most of the patients who had repeated tests.

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The American Academy of Allergy

IN MEMORIAM

RUDOLPH M. HECHT
1906-1944

IN NOVEMBER, 1944, Captain Rudolph M. Hecht, M.C., Army of the United States lost his life during the performance of his duty with an Army base hospital in France.

Born in Chicago on Jan. 1, 1906, Dr. Hecht graduated from the University of Chicago, interned at the Michael Reese Hospital, and, in 1933, received his degree in medicine at the University of Illinois College of Medicine.

He then studied allergy and applied immunology with Dr. Ben Z. Rappaport in Chicago, and dermatology and syphilology at the Skin and Cancer Unit of the New York Post-Graduate Hospital and under the preceptorship of Dr. Marion B. Sulzberger in New York City.

Until the activation of his commission on Oct. 10, 1942, Dr. Hecht practiced in Chicago, and was on the staff of Dr. Francis E. Senear, as Instructor in Dermatology at the University of Illinois and in the University's Research Hospital.

Despite his youth, Dr. Hecht had already achieved a position of great respect in the medical fraternity and in the community at large. His contributions to medical science were of the highest order and included such subjects as the isolation of different allergenic fractions in pollen; the rate of absorption of ingested pollen from the human gastrointestinal tract; the laws governing sensitization of the skin to simple chemicals; the general lack of contagiousness of ringworm of the feet and groins; and experimental sensitizations of rabbits to extracts of homologous skin.

Dr. Hecht was an honored member of many local and national medical societies, and also of the American Academy of Dermatology and Syphilology, The Society of Investigative Dermatology, and the American Association for the Study of Allergy.

Captain Hecht was not only a fine physician and scientist but a true friend and a witty and stimulating companion. His warm heart, excellent sense of humor, uncompromising integrity, and keen intelligence formed a unique combination.

The Academy mourns the loss of a well beloved and highly respected friend and colleague, and extends its heartfelt sympathy to his bereaved wife and to his mother.

MARION B. SULZBERGER
SAMUEL M. FEINBERG

AARON BROWN
1884-1945

AARON BROWN died suddenly Jan. 24, 1945, in New York City at the peak of his professional attainments. He was born July 4, 1884, obtained premedical training at the College of the City of New York, and received the degree of Doctor of Medicine from the Cornell University School of Medicine in 1906.

He was one of the group of physicians who were first to recognize the importance and the significance of clinical sensitization in man, making this subject his special field even before the term "allergy" was generally accepted to describe it. When the Asthma and Hay Fever Clinic of the New York Hospital, then located at 8 West Sixteenth Street, was established by Drs. Robert A. Cooke and Albert VanderVeer, Jr., he became a staff member together with Dr. J. Alexander Clarke, Jr., and Dr. August A. Thommen, both now deceased, and the Chairman of this committee.

He never lost his original zeal and interest in his specialty, as attested by a long list of publications and appointments. He was the Chief Allergist of the Clinic of New York University and Assistant Clinical Professor of Medicine in that institution. He was also an Assistant Visiting Physician at Bellevue Hospital, Consulting Physician at the Bronx Hospital, and Director of the Allergy Service at the Midtown Hospital. He was a past president of the Society for the Study of Asthma and Allied Conditions, a member of the American Immunological Society, the American Therapeutic Society, and a Fellow of the American Academy of Allergy. He was a member of the American Association for the Advancement of Science and a Fellow of the New York Academy of Medicine and of the American Medical Association. He received his certification as a specialist in Internal Medicine in 1937 and in Allergy in 1941. He was an Honorary Member of Sigma Chi.

Dr. Brown's interests were not confined to the practice of medicine. He was the Founder at Cornell, in 1904, during his student days, of the Medical Fraternity, Phi Delta Epsilon, and had held, subsequently, the important posts of Grand Scribe, Grand Chancellor, Grand Consul, and President of the Board of Trustees. He was Editor-in-Chief of the Phi Delta Epsilon News from 1914 to 1945.

Possessed of a charming and pleasing personality, Aaron Brown was a pioneer in his chosen field of allergy and was highly regarded by his fellows. His death means a great loss to his friends and to the medical profession. To his bereaved family the American Academy of Allergy extends its sincerest and deepest sympathy.

W. C. Spain, Chairman
Robert A. Cooke
Albert VanderVeer
Leo H. Criep

News and Notes

A meeting of the Executive Committee was held in Toledo on April 21 and 22. The second annual meeting, scheduled to be held in Chicago in December, was discussed. From information at hand it appears that there is some probability that this meeting may be held, and a program will be assembled. In the event that the meeting be cancelled, presentations accepted by the Program Committee will appear in one or two special program issues of The Journal of Allergy. Announcements of further transactions will be reported later.

The first installment of the official directory of the Academy will appear in the next issue of the Journal. Corrections or omissions should be sent to the Editor immediately.

Publication of the following announcement was requested: "The Society for Investigative Dermatology announces the resumption of publication of its periodical, *The Journal of Investigative Dermatology,* which temporarily suspended publication in 1942 on account of war conditions. The first number of Volume 6 appeared in February. It will be issued bi-monthly, one volume a year, by the Williams & Wilkins Company, Baltimore (2), Maryland."

Book Reviews

Essentials of Allergy. Leo H. Criep, M.D., Philadelphia, 1945, J. B. Lippincott Co., pp. 381, illustrated.

This book is one of the "Essentials" series of the publisher. In the preface the author states that it is meant neither for the specialist in allergy nor for the allergic patient, but is intended as a manual for the undergraduate student, as well as for the practicing physician. The author has achieved his purpose and has produced in this small book a surprisingly complete account of the various aspects of allergy in its conventional sense (illustrated by case reports). It is all there; the immunological considerations, laboratory procedures, clinical aspects, treatment schedules, and a wealth of other material. Most of this is abbreviated to fit into the limited space. For a compendium of this type it is very well done.

This reviewer would like to read a larger work on this subject wherein the opinions of this distinguished author could be elaborated.

Bronchial Asthma. Leon Unger, M.D., Springfield, Illinois, 1945, Charles C Thomas, pp. 724, illustrated.

This is by far the most pretentious book on the subject of bronchial asthma that has been published in recent years. It contains a wealth of information supported by an extensive bibliography. The task of presenting all of this data in an orderly sequence would require very careful planning. At times this is very well done, whereas in parts of the book the author's apparent desire to get everything in has led to such disorganization that sometimes data appear twice (Fig. 12 and Fig. 101 are identical tables). Other "padding" consists of rather meaningless illustrations, as Fig. 47, a healthy smiling child holding a lollipop with the caption stating that his asthma and dermatitis were cured by an oat-free diet. Another is that of a boy with conjunctivitis who, apparently, is about to sneeze. Fig. 16, which almost fills the page, is labelled "48 common causative substances" in pictures, a cat, a carrot, an orange, etc. Figs. 112 and 113 are caricatures of patients with an attack of migraine. Pages 526 to 576 deal with "Other Allergic Diseases," and there is other irrelevant material.

The problem of how to classify known allergic asthma from other types, for which various unsatisfactory designations now exist, as "intrinsic," "non-atopic," etc., was met by a new classification, namely, "paroxysmal asthma" and "chronic asthma." This scarcely clarifies the problem, especially since a considerable number of cases of "chronic asthma" appear in the first decade. These terms offer no clear distinction.

The chapters on the history of asthma and on pathology are excellent. Others dealing with conventional methods of diagnosis and treatment are entirely adequate. The bibliography following each chapter is both ample and relevant.

Were this work largely condensed and all the good material in it presented in an orderly fashion, it would be a significant contribution to the literature.

Announcement

In compliance with the directives imposed by the War Production Board limiting the amount of paper consumed in the production of this JOURNAL, the publishers find it necessary to change the format. As soon as these restrictions are lifted the original format will be restored. Even though the number of pages has been reduced, the actual content of the JOURNAL has not been decreased to any appreciable extent.